TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CADMIUM

PART B:

HEALTH EFFECTS OF CADMIUM

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EXECUTIVE SUMMARY

Executive Summary

Cadmium is a silvery-white metal found primarily in the +2 oxidation state. Although cadmium is not known to be an essential element, it is chemically similar to zinc and other biologically essential elements. This similarity is an important factor in cadmium-induced toxicity since cadmium may replace these essential elements biochemically and interfere with important physiological processes.

For the general population, the major sources of exposure to cadmium are through food and smoking. For occupationally exposed populations, inhalation may be the major route of exposure. Ambient airborne cadmium may also become a significant exposure route in industrial areas.

Although ingestion is the major route of exposure, only one to ten percent of ingested cadmium appears to be absorbed systemically. Pulmonary absorption of inhaled cadmium is estimated to range from 10 to 50 percent of deposited cadmium. Animal studies indicate that some soluble and insoluble cadmium salts are handled in a similar manner in the respiratory tract. Together the liver and kidney account for about 50 percent of the cadmium body burden, with 30 percent found in the kidneys. The biological half-life of cadmium in humans has been estimated to range from 10 to 30 years.

Cadmium has moderate acute toxicity, producing gastrointestinal or pulmonary effects from ingestion or inhalation, respectively. Subchronic and chronic exposures to cadmium have been associated with a wide range of adverse outcomes that include cardiovascular, endocrine, hepatic, bone, hematological, immunological, respiratory, renal, reproductive, and teratogenic effects. The staff of the California Department of Health Services (DHS) has concluded that renal toxicity is the most sensitive noncarcinogenic effect, because it occurs at lower exposure levels than other noncarcinogenic effects.

The staff of the Air Resources Board has estimated that the ambient airborne concentration of cadmium in California is in the range of 1 to 2.5 ng/m^3. A daily retention rate of cadmium estimated to induce renal toxicity in 10 percent of the population has been estimated to be 6.6 to 24.6 μg/day over a 50-year period. Ambient air concentrations necessary to attain this range of retention rates have been estimated to be 650 to 2500 ng/m^3, assuming 50 percent pulmonary absorption. Although no threshold exposure level has been determined for renal toxicity, the staff of DHS believes that such a level does exist. The staff of DHS has concluded that the two to three orders of magnitude difference between the estimated ambient levels of cadmium and those concentrations necessary to attain a retention rate at which 10 percent of the population would develop renal toxicity is sufficiently large that ambient airborne cadmium does not pose a significant hazard. Since renal toxicity is the most sensitive noncarcinogenic endpoint, the staff of DHS does not expect any other acute or chronic noncarcinogenic toxic effects from current ambient levels.

In addition, cadmium has induced cancer in experimental animals and has been associated with an increase in human cancers in epidemiological studies. Cadmium has produced injection site tumors (in rats) and remote tumors (in rats and mice) following subcutaneous or intramuscular injections, and has produced lung tumors in rats exposed to cadmium chloride aerosol. Several studies in which cadmium was given by the oral route have been negative, perhaps because of poor gastrointestinal absorption and low susceptibility of gastrointestinal epithelial tissue to carcinogenesis induced by cadmium. The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of carcinogenicity in animals and that, for practical purposes, cadmium should be regarded as if it presents a carcinogenic risk to humans. DHS staff concurs in these conclusions.

Epidemiological evidence has suggested an association between cadmium exposure and neoplasia, including respiratory, renal, prostatic, and bladder cancers. For the latter three cancers the evidence is suggestive or inconclusive; however, there is strong evidence of an association between cadmium exposure and an increased risk of respiratory cancer. Several occupational studies have shown some association between cadmium exposure or potential exposure and lung cancer. A recently published, well-designed study which evaluated a cohort of cadmium-exposed workers, found a highly statistically significant dose-response relationship. Neither bias nor confounding appeared to be responsible for the observed excess lung cancer risk.

A variety of studies have indicated that cadmium is mutagenic and clastogenic. However, a number of similar studies have given negative

results. Therefore, the staff of DHS has concluded that there is only limited evidence that cadmium is mutagenic and clastogenic.

There is also evidence that cadmium can bind to DNA and cause mispairing of synthetic polynucleotides. This type of activity may also cause a mutagenic or carcinogenic effect. The mechanism of action for this type of effect is postulated to have no threshold associated with it. In the absence of compelling evidence of a threshold, the staff of DHS considers the mechanism of cadmium carcinogenesis to be a nonthreshold process.

The estimated ambient airborne concentrations of cadmium were predicted to present a potential carcinogenic risk to humans. Two separate cancer risk assessments were performed, both of which assumed that cadmium carcinogenicity operates through a nonthreshold mechanism. One was based on a mortality study of workers in a cadmium production plant. A direct linear model that incorporated an adjustment for the "healthy worker effect" was fitted to the exposure data and corresponding standardized mortality ratios for respiratory cancer. The second cancer risk assessment was based on rat lung tumor incidence in a 27-month inhalation bioassay of soluble cadmium chloride aerosol. Several models were fitted to these data, including the multistage model. Predictions of cancer risks at ambient air concentrations in California were obtained by extrapolating 3 to 4 orders of magnitude down from either the experimental rat exposures or the occupational exposures. For continuous lifetime exposure to 1 ng/m^3 cadmium, the human-based assessment predicted the range of excess lifetime cancer risks to be 2 per million (best estimate) to 12 per million (upper 95% confidence limit). The animal-based assessment predicted the range of excess lifetime cancer risks

to be 110 per million (maximum likelihood estimate) to 180 per million (upper 95% confidence limit). The upper 95% confidence limit for risk based on the animal data is about 15 times the upper 95% confidence limit predicted by the human data. The best estimate from the animal data is about ten times the upper 95% confidence limit of risk predicted by the human data. (See Table I-1 and Figure I-1.)

The DHS staff believes that a discrepancy of one to two orders of magnitude between animal- and human-based risk estimates is relatively small. Because the human data for exposure and for response were not found to have any major deficiencies, and because a conservative linear extrapolation was used, DHS staff has determined that reliance on the human-based risk assessment is unlikely to underestimate risk. The range of recommended risk estimates is therefore provided by the human-based risk assessment.

The hazard posed by atmospheric cadmium to residents of California was estimated by applying the risk estimate to cadmium concentrations measured in the state. Noncancer health effects are not expected to occur at concentrations of cadmium measured in populated areas of the state. In contrast, carcinogenic effects may occur at levels of cadmium measured in ambient air. The upper-bound excess lifetime cancer risk from estimated atmospheric concentrations of cadmium in California has been estimated to range from 2 per million to 30 per million. This is a health-conservative estimate; the actual risk may lie in or below that range.

DHS staff emphasizes that the risk estimates derived in conducting a risk assessment are not exact predictions, but rather represent best estimates

based on current scientific knowledge and methods. Uncertainty in this risk assessment stems from (1) limitations in the data on which the assessment was based, (2) an extrapolation from occupational exposure levels to current ambient cadmium concentrations ranging over three to four orders of magnitude, (3) generalization from the mortality experience of adult white males in Colorado to the general population in California, (4) differences between occupational and nonoccupational exposures in terms of particle size distribution, and (5) potential inaccuracy and variability of ambient exposure measurements.

The DHS staff has determined that the possible roles of chance, bias and/or confounding in distorting the true dose-response relationship in the occupational study were likely to have been small. The DHS staff has also concluded that inaccuracies in the evaluation of exposure and cancer mortality in that study were likely to have been small. In addition, the net direction of these potential errors was likely to result in an overestimate of cadmium's potency. For these reasons, the DHS staff believes that the use of these epidemiologic data in a quantitative risk assessment is appropriate. Furthermore, the use of human data eliminates uncertainty arising from interspecies extrapolation. Since the occupational exposures were by inhalation, there is no extrapolation between routes of exposure.

The DHS staff recommends that the range of risks for ambient exposures to cadmium be based on the best estimate and upper 95% confidence limit predicted from fitting a linear model to the human data. The range of estimated excess lifetime cancer risks from 24-hour-per-day exposure for a

lifetime to average ambient airborne concentrations, estimated to be 1 to 2.5 ng/m^3 cadmium, is 2 to 30 per million persons exposed. In "hot spots" identified in California, the range of estimated excess lifetime cancer risks from 24-hour-per-day exposure for a lifetime to an average of 40 ng/m^3 of cadmium is 80 to 480 per million persons exposed. The ARB staff has estimated that approximately 57,000 people may be exposed to the average hot spot ambient level.

Based on the finding of cadmium-induced carcinogenicity and the results of the risk assessment, DHS staff finds that ambient cadmium is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

TABLE I-1

ANIMAL AND HUMAN BASED PREDICTIONS

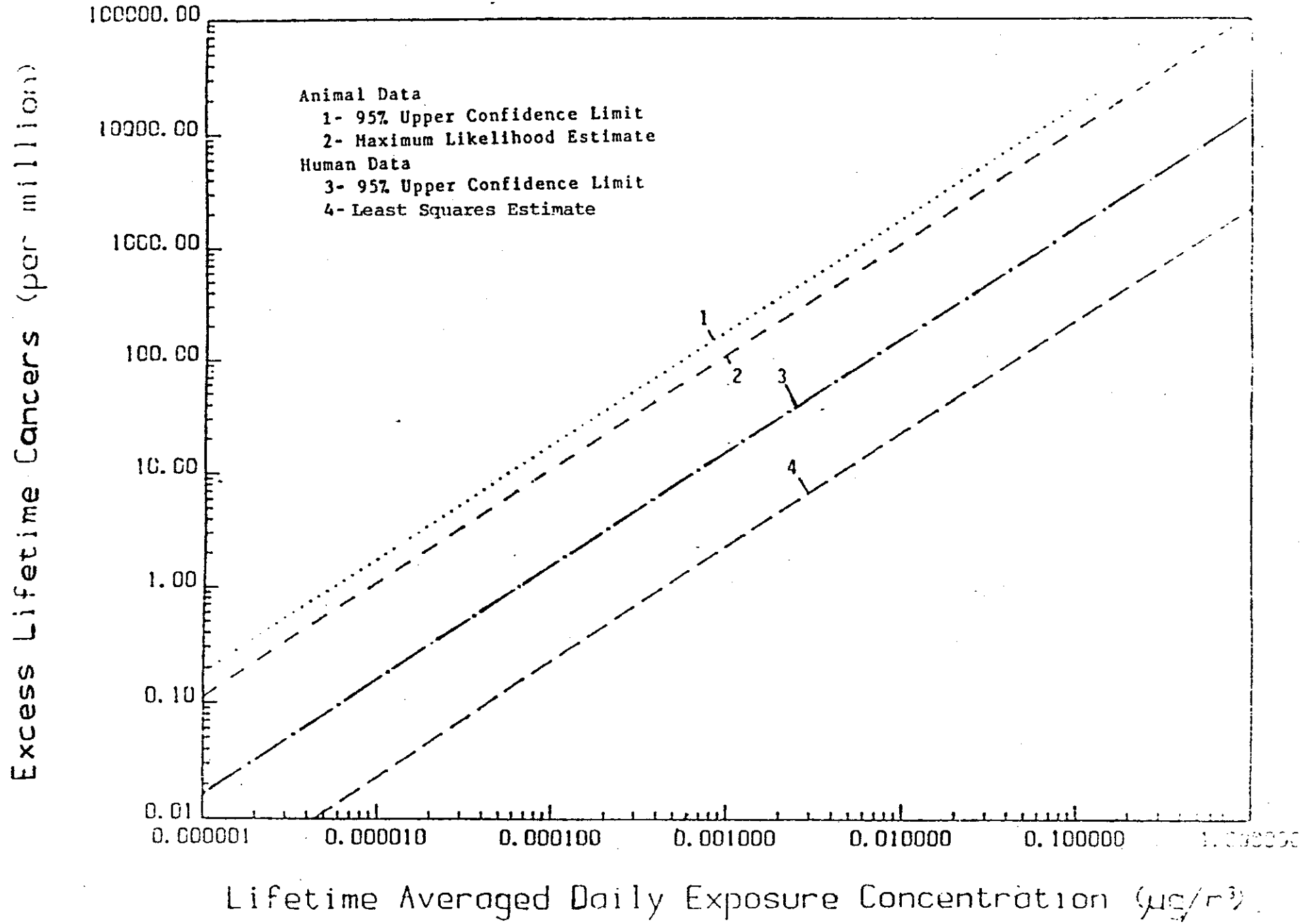
OF EXCESS LIFETIME CANCER RISKS PER MILLION PERSONS

EXPOSED TO AMBIENT AIRBORNE CONCENTRATIONS OF CADMIUM

	Ambient Air Concentration		
	1 ng/m^3	2.5 ng/m^3	40 ng/m^3
	Overall mean in California	UCL of overall California mean	hot spot mean
ANIMAL DATA			
95% Upper Confidence Limit	$180/10^6$	$450/10^6$	$7200/10^6$
Point Estimate	$110/10^6$	$275/10^6$	$4400/10^6$
HUMAN DATA			
95% Upper Confidence Limit	$12/10^6$	$30/10^6$	$480/10^6$
Point Estimate	$2/10^6$	$5/10^6$	$80/10^6$

Figure I-1

ESTIMATES OF HUMAN EXCESS LIFETIME CANCER RISK BASED ON ANIMAL AND HUMAN DATA



II. Introduction

Cadmium was first identified as a distinct element in 1817. During the 1800s there were some reported cases of cadmium poisoning from inhalation of cadmium fumes or dust; however, it was not until the second or third decade of the present century that cadmium was recognized as a significant occupational health problem. Occupational exposure has been associated with acute and chronic respiratory effects and renal toxicity. Environmental exposure to cadmium has been considered to play an etiological role in Itai-Itai disease, a disease where the patients have severe osteoporosis and osteomalacia. Many other toxic effects in humans and experimental animals have now been associated with cadmium exposure.

There has been a tremendous effort to study the adverse effects of cadmium, and a vast literature on the subject has accumulated. This literature has been reviewed and evaluated by many authors. Some of the most comprehensive reviews are by Friberg et al. (1974) and EPA (1981, 1985). These reviews are referred to extensively in the present document.

III. Properties and Uses

Cadmium is a relatively rare element that makes up about 1.5×10^{-5} percent of the earth's crust. It is a transition element in group 2b of the periodic table, which also includes zinc and mercury. This chemical similarity between cadmium and zinc is an important factor in cadmium toxicity, as will be discussed in the document. Cadmium is usually obtained as a by-product from the processing of zinc, lead, and copper ores, where it is primarily found as cadmium sulfide. The elemental form of cadmium is a soft silvery-white metal that has a molecular weight of 112.4. Its most common oxidation state is +2, although a few compounds have been reported in which cadmium is in the +1 oxidation state (Hollander and Carapella 1978). Cadmium salts, as with most metal salts, range from highly water soluble to insoluble (see Table III-1). The predominant form of cadmium found in air pollution is cadmium oxide, although other forms may be present.

Cadmium has a number of economic uses, such as in metal finishing, pigments, batteries, stabilizers in plastics, electronic application, and catalysts. The major use is in the electroplating industry, which accounts for over half of the cadmium usage in the United States (Parker 1978).

The major source of cadmium release to the environment is from solid wastes, such as coal ash, sewage sludge, flue dust, and fertilizers (Parker 1978). An increasingly greater source of cadmium release is from plastics burned in municipal waste incinerators (Yost 1979).

Table III-1

Some Physical Properties of Selected Cadmium Compounds[a]

Chemical Name	Formula	Molecular Weight	Water Solubility ($g/100gH_2O$/Temp°C)
Cadmium	Cd	112.4	Insoluble, soluble in dilute nitric or sulfuric acid
Cadmium acetate	$Cd(C_2H_3O_2)_2$	230.5	Soluble
Cadmium carbonate	$CdCO_3$	172.4	Insoluble (2.8×10^{-6}), soluble in acids
Cadmium chloride	$CdCl_2$	183.3	Soluble (128.6/30)
Cadmium fluoride	CdF_2	150.4	Soluble (4.35/25)
Cadmium nitrate	$Cd(NO_3)_2$	236.4	Soluble (109/0)
Cadmium oxide	CdO	128.4	Insoluble (9.6×10^{-4}), soluble in acids
Cadmium sulfate	$CdSO_4$	208.5	Soluble (76.6/20)
Cadmium sulfide	CdS	144.5	Insoluble (1.3×10^{-4}/18), soluble in acids

[a] Source: IARC 1976, Hollander and Carapella 1978

IV Routes of Exposure

A. Food and Smoking

The major exposures to cadmium are through food and smoking. Several food crops, including potatoes, root crops, and leafy vegetables, are known to take up and concentrate cadmium from the soil (Pahren et al. 1978). Daily intake of cadmium from food and water has been estimated to be 39 μg/day for a 15-to 20-year-old male (FDA 1974).

Smoking can contribute a significant proportion of an individual's daily exposure to cadmium. It is estimated that 0.1 to 0.2 μg of cadmium are inhaled with each cigarette (EPA 1980a). Therefore, smoking one pack per day (20 cigarettes) can increase the daily cadmium intake by about 10% (2 to 4 μg/day).

B. Occupational

Occupational exposure is primarily through inhalation of airborne cadmium. It is the greatest source of exposure for this cadmium worker population. The present OSHA standards for occupational exposure are 100 $\mu g/m^3$ for cadmium fumes and 200 $\mu g/m^3$ for cadmium dust on a time weighted average for an eight-hour workday (NIOSH 1984a). The American Conference of Governmental Industrial Hygienists (ACGIH 1984) has established the Threshold Limit Value (TLV) for an eight-hour exposure at 50 $\mu g/m^3$. NIOSH has recommended that the standard be set at 40 $\mu g/m^3$ for a time weighted average of a 10-hour workday, 40-hour workweek (NIOSH 1984a). Assuming an

average air intake of 10 m^3 during the working day, daily exposure could range from 400 to 2000 μg of cadmium if exposures occurred at levels between the NIOSH recommended level and the current OSHA standard.

C. Pollution

Environmental pollution can increase cadmium exposure via ingestion and inhalation. Cadmium soil levels in crop lands can be increased by use of phosphate fertilizers or municipal sludge, both of which contain high levels of cadmium. Deposition of airborne cadmium on crop land can also increase cadmium soil levels.

Airborne cadmium is primarily from anthropogenic sources. Highest levels are found in industrialized cities and around smelting operations. When no significant sources of cadmium pollution are present the airborne concentration is generally around 1 ng/m^3 (EPA 1980a). Assuming an average daily inhalation volume of 18 m^3, the daily exposure from ambient air would be about 20 ng.

V. Pharmacokinetics and Metabolism

Inhalation is the primary route of exposure to airborne cadmium. However, swallowing particulates initially deposited in the upper respiratory tract may also play a role in exposure to inhaled cadmium. Airborne cadmium is primarily found as the oxide, although other insoluble and soluble salts may be present. These salts can be pure or a mixture in an aerosol or in dust. The deposition of cadmium in the respiratory system is dependent on the size of inhaled particles.

The Task Group on Lung Dynamics (1966) defined the different portions of the respiratory system as: (1) the nasopharynx, which begins with the anterior nares and extends to the larynx or epiglottis, (2) the tracheal/bronchial portion, extending from the trachea to the terminal bronchioles, and (3) the pulmonary portion, which extends from the respiratory bronchioles to the alveolar sacs. Deposition in the pulmonary portion of the respiratory system is usually of greatest concern because clearance is much slower than in the other portions. Large particles (10 to 100 μm) tend to be almost completely removed in the nasopharynx. Particles of 5 to 10 μm still tend to be trapped in the nasopharynx, but 5 to 25 percent may be deposited in the pulmonary portion. About 20 to 30 percent of particles from 0.5 to 5 μm are deposited in the pulmonary portion and up to almost 70 percent of smaller particles may be deposited. Some small particles (0.1 to 0.5 μm) may be exhaled. In a person breathing at a moderate work rate (20 liters/min), about 10 to 60 percent of particles with a mass median diameter of 0.01 to 5 μm would be deposited in the pulmonary compartment (Task Group

on Lung Dynamics 1966). The model used by the Task Group assumed nasal breathing only. Deposition may be greater in the pulmonary portion when breathing occurs through the mouth. Milford and Davidson (1985) estimated the proportion of cadmium deposition in the pulmony compartment during mouth breathing. They estimated 11 to 27 percent of the airborne cadmium would be depositied using respiration rates of 7.5 to 30 liters per minute. Particle size distribution was based on measurements from a number of different studies at a variety of locations. The mass median aerodynamic diameter in this analysis was 0.84 μm.

Particles trapped in the upper respiratory tract and those deposited on tracheal and bronchial mucosa will be cleared by mucociliary activity and swallowed. Some particles deposited in the lower respiratory tract may be phagocytized by pulmonary macrophages and transported out of the lung by mucociliary activity. Thus, absorption of cadmium from the lung and gastrointestinal tract both need to be considered. In addition, the greatest source of cadmium exposure for the general population is via food, which makes the gastrointestinal tract the primary site of cadmium absorption.

A. Absorption from the Lungs

Friberg et al. (1974) reviewed several animal inhalation studies and a study comparing the body burdens of cadmium in smokers versus nonsmokers, then estimated the proportions of cadmium absorbed. From acute exposure studies on dogs (Harrison et al. 1947) and mice (Potts et al. 1950), they estimated absorption of 40 and 10 percent, respectively. A 30 percent absorption was estimated from a chronic exposure study in rabbits (Friberg 1950). The

cadmium body burden in smokers (Lewis et al. 1972) suggested that absorption was as high as 27 percent. EPA (1981) cites a reference (Task Group on Lung Dynamics 1966) that indicates absorption of cadmium from human lungs could range from less than 20 to 50 percent, depending on particle size, solubility, and other factors.

Absorption may be dependent on the solubility of the chemical form of the inhaled cadmium; however, some animal studies suggest otherwise, at least for cadmium chloride and cadmium oxide. Oberdorster et al. (1979) compared the lung clearance of cadmium chloride and cadmium oxide in rats following administration via inhalation. Since the aerosols of both compounds had similar particle size distributions and were administered at similar airborne concentrations, solubility was the major variable. The difference in solubility did not prove to have a significant effect on long-term clearance from the lung since both cadmium compounds had half-lives of 67 days. Short-term clearance was not observed for cadmium chloride, but was seen for cadmium oxide. In a later study, however, Oberdorster et al. (1980) reported short-term lung clearance of cadmium chloride. Oberdorster et al. (1979, 1980) interpreted the similar long-term clearance of the two compounds from the lung as indicating that both compounds were handled in the same manner. They suggested that in both cases cadmium protein binding may be involved and followed by absorption via alveolar clearance pathways.

Short-term clearance would probably include bronchial clearance and cadmium would end up in the gastrointestinal tract. However, Hadley et al. (1980) found that a large amount of the intratracheally instilled cadmium oxide that was removed from rat lungs during short-term clearance was found in the liver. This indicates that much of the cadmium oxide was solubilized and

absorbed systemically. Since absorption from gastrointestinal tract is limited, as will be discussed in Section V.B, much of the short-term clearance must be from pulmonary absorption.

The extent of short-term clearance for cadmium oxide that was observed by Hadley et al. (1980) was greater than that for cadmium chloride observed by Oberdörster et al. (1980) following intratracheal instillation. The reason for the difference has not been examined.

Friberg et al. (1974) has concluded from a review of the available information that animal experiments indicate 10 to 40 percent of inhaled and deposited cadmium is absorbed from the lung. Information on absorption from human lungs of cadmium in cigarette smoke indicates that it is from 25 to 50 percent. Thus, a range of 10 to 50 percent of inhaled cadmium deposited in the lung may be systemically absorbed.

B. Absorption from the Gastrointestinal Tract

Several animal studies have been performed to determine the magnitude of cadmium absorption from the gastrointestinal tract. These studies, reviewed by Friberg et al. (1974), indicate that most ingested cadmium, about 96 to more than 99%, is not absorbed and is excreted in the feces. Human studies, also reviewed by Friberg et al. (1974), indicated that absorption was from 1 to 10 percent of ingested cadmium.

Factors found to influence cadmium absorption from the gastrointestinal tract include age and nutrition. Engström and Nordberg (1979) report that one-month-old mice retained 5.2% of an orally administered dose while three-

and six-month old mice retained only 2.9 and 2.1% of administered doses, respectively. Several studies have shown that a calcium deficient diet causes an increased cadmium uptake by the gastrointestinal tract, and one study suggested that vitamin D increases cadmium uptake (Friberg et al. 1974). Low protein diets have been found to increase the amount of cadmium absorbed (Suzuki et al. 1969).

C. Distribution and Storage

Once cadmium is absorbed it enters the circulatory system. Animal studies indicate that cadmium will initially be found in the plasma. Levels in the plasma fall rapidly, but then cadmium levels in the red blood cells rise. Cadmium associated with the red blood cells is bound to proteins such as metallothionein and hemoglobin. Continuous exposure produces an increase in the concentration of cadmium in the blood, but a plateau occurs at a certain blood level. When exposure ends cadmium blood levels will decrease (Friberg et al. 1974).

Together the liver and kidney account for about 50 percent of the cadmium body burden, with 30 percent found in the kidneys. Other organs in which cadmium accumulates are the spleen, pancreas and testes (Probst 1979). Initially the concentration of cadmium increases faster in the liver than the kidney. In the liver most cadmium is bound to a low molecular weight protein, metallothionein. This protein bound cadmium is believed to be the form in which cadmium is redistributed from the liver to the kidney (Norberg 1972, Tanaka et al. 1975). Within the kidney the highest concentration of cadmium is found in the cortex. The level of cadmium in the renal cortex

increases until renal toxicity occurs, at which point urinary cadmium excretion will increase and renal cortex levels decrease. This is from a lack of uptake of cadmium-bound metallothionein by damaged renal tubular cells and the loss of cadmium in sloughed renal tubular cells.

D. Excretion

Generally, excretion of absorbed cadmium is very slow because little cadmium is lost in the urine since there is efficient uptake by the renal tubular cells. In mice, daily renal excretion accounts for about 0.01 to 0.02 percent of the total body burden. Animal studies have been been conducted to estimate the biological half-life of cadmium. It was found to vary from about 200 days in mice to 1.5 years in squirrel monkeys. The biological half-life of cadmium in humans has been estimated using mathematical models to range from 10 to 30 years (Friberg et al. 1974).

E. Metallothionein Binding

Metallothionein is a small molecular weight protein that appears to play an important role in cadmium's metabolism. Two distinct forms of this protein are usually found in tissues. They differ slightly in amino acid composition (Winge and Meklossy 1982). Metallothionein can bind cadmium, zinc, copper and mercury. The relative affinities of rat kidney metallothionein for these four metals are in the order of mercury>copper>cadmium>zinc (Foulkes 1982). This is probably the same order found for metallothionein in other tissues and species.

Metallothionein is in many tissues, with the highest concentrations found in the liver and kidney, where the highest levels of cadmium are also found. Most of the cadmium (80%) in these two organs is bound to metallothionein. In the kidney most metallothionein contains cadmium and zinc, followed by copper (Kagi et al. 1984). As the cadmium concentration in the kidney increases, there is a proportional increase in the concentration of zinc (Friberg et al. 1974). At high cadmium concentrations, the zinc concentration no longer increases.

Metallothionein synthesis is induced when cadmium or zinc is given pareterally. Induction is greatest in the liver, although it is also induced in other tissues such as the kidney and pancreas. The biological halflife of metallothionein has been found to be relatively short (5 days or less), especially when compared to the biological half-life of cadmium. Thus, cadmium and zinc ions are released by degradation of the protein and then are bound to new metallothionein that is constantly being synthesized.

The physiological role of metallothionein is not fully understood. Metallothionein is probably a transport and storage protein for trace elements, such as zinc and copper, that are essential for many physiological functions. Because cadmium is chemically similar to these essential elements, metallothionein can effectively detoxify cadmium by binding with it, but metallothionein enables the body to efficiently store cadmium until it becomes a problem.

When cadmium is combined with metallothionein, it is less toxic to many target organs. Injections of cadmium-bound metallothionein did not cause testcular damage in animals while a similar dose of cadmium chloride did.

However, cadmium-bound metallothionein is more toxic to the kidney than is cadmum chloride (Nordberg 1971). This is in part explained by the fact that most free cadmium is taken up by the liver and only a small percentage (10%) is found in the kidney whereas about 90% of the metallothionein bound cadmium ends up in the kidney. Since metallothionein is freely filterable by the glomerulus and is then actively reabsorbed from tubular fluid, high levels of free cadmium are likely to occur in the tubular cells following degradation of the metallothionein protein. The lack of sufficient new unbound metallothionein to bind with free cadmium allows the latter to produce a toxic effect on the cells. This is similar to the mechanism proposed for renal toxicity following chronic exposure to cadmium.

VI. Acute Health Effects

Cadmium has a moderately acute toxicity with a oral LD_{50} in rats that varies from 72 to over 225 mg/kg depending on the chemical form (see Table VI-1). The toxic effects observed in humans differ depending on whether the route of acute exposure is via ingestion or inhalation. Symptoms in humans following ingestion of acutely toxic levels of cadmium include persistent vomiting, increased salivation, choking sensation, abdominal pain, tenesmus, and diarrhea (EPA 1980a). These symptoms may occur within 15 to 30 minutes of ingestion.

Exposure to acutely toxic airborne concentrations of cadmium (see Table VI-1) may produce symptoms in humans within 4 to 6 hours that include cough, shortness of breath, and tightness of the chest. Acute pulmonary edema may follow within 24 hours. From 3 to 10 days after exposure, proliferative interstitial pneumonitis may occur. In rats a fourth stage occurs which involves permanent lung damage in the form of perivascular and peribronchial fibrosis (EPA 1980a).

Both routes of exposure have led to systemic signs of toxicity that include renal and liver toxicity in both humans and experimental animals. Animal studies have also indicated that acute exposure to high levels of cadmium can lead to testicular and placental necrosis and other reproductive effects. Reproductive effects are further discussed in Section VII.I.

Table VI-1

Selected Acute Toxicity Data[a]

Compound	Species	Route	Effect[b]	Dose
Cadmium (colloidal)	Rat	Oral	LD_{50}	225 mg/kg
Cadmium chloride	Rat	Oral	LD_{50}	88 mg/kg
Cadmium fluoroborate	Rat	Oral	LDLo	250 mg/kg
Cadmium fluorosilicate	Rat	Oral	LDLo	100 mg/kg
Cadmium oxide	Rat	Oral	LD_{50}	72 mg/kg
Cadmium oxide	Rat	Inhalation	LCLo	10 mg/m^3
Cadmium oxide fumes	Rat	Inhalation	LC_{50}	500 mg/m^3/10 min
Cadmium	Human	Inhalation	LCLo	39 mg/m^3/20 min
Cadmium oxide fume	Human	Inhalation	LCLo	2500 mg/m^3[c]
Cadmium oxide fume	Human	Inhalation	TCLo	8.6 mg/m^3/5 hour

[a] Source: NIOSH 1984b

[b] LD_{50} - dose that is lethal to 50 percent of the experimental population
LDLo - lowest dose to produce a lethal effect in the experimental population
LCLo - lowest airborne concentration to produce a lethal effect in humans or in the experimental population
LC_{50} - airborne concentration that is lethal to 50 percent of the experimental population
TCLo - lowest dose to produce a toxic effect in humans or in experimental populations

[c] Although the dose was given in NIOSH (1984b) as 2500 mg/m^3, the actual reported dose was 2500 minutes x mg/m^3 Barrett and Card (1947) estimated that the lethal concentration was 2900 minutes x mg/kg. For an 8 hour work day the airborne concentration would be 5 mg/m^3 and for a 24 hour period the airborne concentration would be 2 mg/m^3.

VII. Subacute and Chronic Health Effects

A. Cardiovascular Effects

Cadmium has been found to induce hypertension and myocardial changes in experimental animals. Friberg et al. (1974) and EPA (1981) have reviewed the literature on these responses in experimental animals and humans. The hypertensive effect of cadmium occurs after chronic low-level oral exposure, but a transient hypertensive reaction can be induced by an acute parenteral administration. Perry et al. (1977) found that exposure through drinking water containing 0.1 to 5 ppm cadmium induced hypertension in rats that were exposed for 18 months. An exposure level of 0.01 ppm had no effect and high exposure levels of 10 and 25 ppm did not have a hypertensive response. The mechanism behind this reaction has not been determined, but may be related to renal toxicity or to an effect on the vasculature. Zinc antagonizes this effect of cadmium.

Cadmium exposure was also found to affect the electrocardiogram recordings of rats treated for 24 weeks with drinking water containing 5 mg of cadmium/liter. Biochemical changes were noted in the myocardium of rats treated with cadmium drinking water concentration as low as 1 mg/liter (Kopp et al. 1978, 1983).

Epidemiological studies have not found a statistically significant association between cadmium exposure and hypertension. Inskip et al. (1982) reported nonsignificantly elevated SMRs for hypertensive deaths

for residents in a town with high soil cadmium content while the control town had a deficit of such deaths. The rate ratios were greater than two for males, females, and both sexes combined. In another epidemiologic study which reported on hypertensive deaths among cadmium-exposed workers, Armstrong and Kazantzis (1983) observed no deaths (.7 expected) in the "ever high" exposure group and a nonsignificant increased risk in the "ever medium" (SMR=178) and the "always low" groups (SMR=113). While these results are suggestive, they do not permit any generalization.

Cerebrovascular deaths were significantly elevated among females in the exposed town from the study of Inskip et al., but deaths from this same cause were reduced in all exposure categories in the study by Armstrong and Kazantzis (significantly so for those with "always low" exposures). Cadmium does not appear to increase the risk of cerebrovascular death.

B. Endocrine Effects

There is some evidence from experimental animal and human studies suggesting that cadmium can affect on endocrine organs (EPA 1981). As will be discussed in Section VII.I, cadmium can cause testicular necrosis at high doses. Since Leydig cells, the androgen producing cells in the testes, are damaged, testosterone synthesis is decreased or abolished until tissue regeneration occurs.

As noted above, the pancreas accumulates cadmium. Glucose intolerance and reduced levels of circulating insulin are associated with cadmium

exposure. Insulin secretion was decreased in rats given intraperitoneal injections of 0.5 mg/kg every other day for 70 days. A dose level of 0.25 mg/kg had no effect (Ithakissios et al. 1975). Selenium and cadmium pretreatment have been found to antagonize this effect.

Cadmium has also been shown to increase adrenal gland weight, adrenal secretion of catecholamines and corticosterone plasma levels in experimental animals. These effects occurred following repeated parenteral administration of doses of 0.25 mg/kg or more of cadmium (Rastogi and Singhal 1975: Der et al. 1977).

Similar dose levels have been associated with decreased plasma T_4 and T_3 levels. There were no morphological changes observed in the thyroid to associate with the plasma level changes (Der et al. 1977).

Repeated intramuscular injection of 250 μg of cadmium chloride for 54 days caused a significant decrease in rat pituitary weight (Der et al. 1977). Some effects observed in the pituitary may, however, be secondary to other endocrine effects caused by cadmium.

C. Hepatic Effects

Several investigators have reported hepatotoxicity in experimental animals exposed to cadmium over long time periods. Rabbits given a 0.25 mg/kg dose of cadmium by injection five days a week for up to 29

weeks had an increase in serum glutamic-oxaloacetic-transaminase (GOT) actively after 17 weeks of exposure (Axelsson and Piscator 1966). At a subcutaneous dose level of 2 mg/kg, 6 days a week for 2 weeks, rabbits had increased serum GOT and glutamic pyruvic-transaminase activities and there were morphological changes in the liver (Kimura 1971). Morphological liver changes without changes in liver function tests, have been reported by Stowe et al. (1972) in rabbits given drinking water containing 160 ppm cadmium for 6 months. Some liver enzyme changes have occurred in rats treated with cadmium via drinking water at 1 ppm (Sporn et al. 1970).

Pronounced changes in liver function are unusual findings in cadmium exposed workers, however, this has not been a major focus of most epidemiological studies (Friberg et al. 1974).

D. Mineral Metabolism

Chronic exposure to cadmium has an adverse effect on calcium and phosphorus metabolism manifested through an observed effect on bone. Bone changes in rats given drinking water containing 50 ppm cadmium had reduced urinary calcium and phosphorus levels and fat deposition in the femoral spongiosa. Treated animals on a calcium deficient diet had thinning of the cortical osseous tissue, osteoid borders on trabeculae, and a decreased number of osteocytes, and a decrease of acid mucopolysacchrides in epiphyseal cartilage (Itokawa et al. 1974). Osteomalacia and severe osteoporosis in humans have been associated with both occupational and environmental exposure. These are the most

prominent effects of Itai-Itai disease. Patients with this disease generally have hypochronic anemia and renal disfunction (proteinuria, glucosuria, and aminoaciduria) as well as skeletal abnormalities. The disease has been confined primarily to a Japanese population (mostly post-menopausal women) residing in an area that is highly contaminated with cadmium. Although the average daily lifetime cadmium intake is not known, the highest intake estimates are over 1 mg/day for at lease part of their lifetime. The disease is believed to be caused by cadmium's renal toxicity disturbing calcium and vitamin D metabolism, but there is evidence that calcium and vitamin D deficiencies may play an etiological role.

E. Hematological Effects

Cadmium does not appear to have strong effects on the hematopoietic system, although animal studies have indicated cadmium can induce a reduction in hematocrit and hemoglobin levels of chronically exposed experimental animals (EPA 1981). Administration of supplemental iron has restored hemoblogin and hematocrit levels. Friberg et al. (1974) reviewed a few epidemiological studies on cadmium-exposed workers where it was found these workers had a moderate anemia.

Decker et al. (1958) found that rats given drinking water containing 0.5 to 1 ppm cadmium for 1 year had normal hemoglobin levels while rats given drinking water containing 50 ppm cadmium for 3 months had low hemoglobin levels. Mahaffey et al. (1981) report that rats fed a diet containing 50 ppm of cadmium for 10 weeks had reduced bone, kidney, and

liver iron levels, suggesting that cadmium may have an affect on iron metabolism.

F. Immunological Effects

Cadmium has been found to decrease the number of antibody-forming spleen cells in mice exposed subchronically via drinking water to 3 or 300 ppm (Koller et al. 1976). In an unplanned study, it was noted that mice being treated with cadmium at 3 and 300 ppm in their drinking water had a higher mortality following an accidental intestinal infection from Hexomita muris than did untreated mice (Exon et al. 1975). Cadmium has also been found to decrease thymus and spleen weights of mice injected with doses of 0.75 to 6 mg/kg. There was also suppression of the induction of delayed hypersensitivity responses and decreased memory T-cell and B-cell activities (Kojima and Tamura 1981).

G. Respiratory Effects

Emphysema and bronchitis are the primary respiratory effects reported from chronic inhalation exposure to cadmium. A causal relationship was first reported by Friberg (1950) who noted this effect in workers exposed to cadmium oxide dust. Since then the results of several epidemiological studies on cadmium-exposed worker populations have confirmed this finding. Several animal studies provide supporting evidence that cadmium causes emphysematous type changes in the lungs. These studies have been reviewed by Friberg et al. (1974) and EPA (1981).

Friberg (1950) exposed rabbits to cadmium iron oxide dust at an airborne concentration of 8 mg/m^3 for 3 hours per day, 20 days per month over an eight-month period. All exposed rabbits showed signs of emphysema and inflammatory changes. Prigge (1978) exposed rats to cadmium oxide at a much lower airborne concentration--25 to 50 μg/m^3 (as cadmium)--24 hours a day for 90 days. Emphysematous areas and cell proliferation of the bronchi and bronchioli were found in all of the exposed animals. This finding, however, is in contrast to the absence of reported emphysematous changes in rats exposed to cadmium chloride at concentrations of 13 to 51 μg/m^3 (as cadmium)--23.5 hours per day for 18 months and then followed for an additional 13 months (Takenaka et al. 1983).

Two reports indicated that rats given cadmium (17.2 mg/liter) in their drinking water for up to 10 months developed emphysematous changes (Miller et al. 1974, Petering et al. 1979). Petering et al. (1979) reported that supplemental zinc in the animals' diet decreased the severity of the changes.

Human studies have, for the most part, been done in the occupational setting. A large number of these studies, reviewed by Friberg et al. (1974) have shown that there are significant changes in pulmonary function tests in groups of exposed workers. Many of these studies did not control for smoking. Since cigarette smoke contains significant amounts of cadmium and there is an association between smoking and emphysema and bronchitis, Friberg et al. suggest that there is reason to believe that smoking may be of importance. Friberg et al. also

observe that, "For cadmium oxide fumes, a prolonged industrial exposure to below 0.1 mg/m^3 might well be considered hazardous with reference to emphysema."

Human studies of the effect on respiratory disease mortality are not consistent. The two findings which were statistically significant were those by Varner (1983) who found a PMR (proportional mortality ratio) of 153 for nonmalignant respiratory disease, and by Armstrong and Kazantzis (1983) who found an increased risk for bronchitis standardized mortality ratio or SMR = 434 for those with "ever high" exposure, SMR = 130 for entire cohort. There was a dose-response relationship with both intensity and duration of exposure, though other exposures may also have played a role. The SMR for nonmalignant respiratory disease showed a nonsignificant but elevated risk in the early cohort of Lemen et al. (1976) (SMR = 159) and in the followup by Thun et al. (1985) (SMR = 154), but these are only modified versions of the cohort Varner studied. Andersson et al. (1984) noted two lung disease deaths with unusual diagnoses that were considered potentially related to cadmium exposure.

Negative findings were reported by Andersson et al. (1984), and Sorahan and Waterhouse (1983). This latter study showed a lower SMR (107) for men employed earlier (when exposures were higher) than for those employed later (128). The ecological study by Inskip et al. (1982) of a town with high cadmium soil content showed extreme deficits (statistically significant) for "all respiratory diseases", in comparison to all of England and Wales, and also in comparison to a

similar nearby town with no exposure to cadmium. However, the exposure in this town was believed to be by ingestion of food grown in contaminated soil, rather than by inhalation.

In an epidemiological study not reviewed by Friberg et al. (1974), workers from different factories, an electronic workshop, a nickle-cadmium storage battery factory, and two cadmium-producing plants, were used to examine pulmonary effects (Lauwerys et al. 1974, 1979). Control groups for each factory were selected and matched according to sex, age, weight, height, smoking habits, and socio-economic status. Two groups of exposed male workers were formed. One group consisted of workers who had been was exposed to cadmium dust and fumes for less than 20 years with an average length of 7.5 years. The second group was made up of workers who had been exposed an average 27.5 years primarily to cadmium oxide fumes. The highest respiratory dust levels (undefined) measured in these factories ranged from 21 to 65 $\mu g/m^3$. Both exposure groups had statistically significant decreases in spirometric indices of forced vital capacity, forced expiratory volume in one second, and peak expiratory flow rate compared to the respective controls. These changes were considered to indicate a mild form of obstructive lung disease.

In a second study, Lauwerys et al. (1979) did a more detailed lung function test on a group of 18 cadmium workers with more than 20 years (average 32 yrs) of exposure. At the time of the study measured total airborne cadmium ranged from 3 to 67 $\mu g/m^3$, but some workers may have been exposed to levels higher than 350 $\mu g/m^3$ prior to 1970. The only

statistically significant changed compared to matched controls was in closing capacity. Although a number of parameters indicating obstructive lung disease were found to differ from control values, the changes were not statistically significant. The authors conclude that the functional impairments observed from chronic cadmium inhalation exposure are only slight compared to the renal effects that were also studied.

A group of non-smoking female workers with an average exposure period of 4.4 years at total airborne cadmium concentration of 10 $\mu g/m^3$ (4 $\mu g/m^3$ respirable dust level) was also examined by Laurwerys et al. (1979). There were no significant lung function changes found for the exposed group compared to a matched control group. The negative finding may be due to the lower exposure level or shorter exposure period.

Both animal and human studies have found pulmonary effects at airborne concentrations of around 20 $\mu g/m^3$. No effects were found in an animal chronic inhalation study at levels of 13 to 51 $\mu g/m^3$ nor in a human study at an average exposure level of 4 $\mu g/m^3$ for an average of 4.4 years.

H. Renal Effects

Cadmium-induced renal toxicity has been found in experimental animals and in both occupationally and nonoccupationally exposed populations. This effect has received the greatest amount of attention because it has been determined to be one of the most sensitive adverse effects

caused by chronic cadmium exposure (Friberg et al. 1974: EPA 1981). The literature on renal toxicity has been reviewed by Friberg et al. (1974), Kawai et al. (1976), and EPA (1981). Because this effect has been so well-documented, the following discussion will just briefly describe cadmium-induced renal toxicity, the postulated mechanism, and levels of cadmium needed to induce this effect.

The earliest clinical sign of cadmium induced renal toxicity is proteinuria, which occurs in both experimental animals and humans (Friberg et al. 1974). The increase in protein excretion is believed to be related to renal tubular damage caused by cadmium which interferes with protein reabsorption from tubular fluid, a metabolically active process. The early stage of this proteinuria is characterized by the relatively large increase of low molecular weight proteins and the relatively small increase of large proteins like albumin that are excreted and is classified as tubular proteinuria. Clinically, the low molecular weight protein β_2-microglobulin is used as a marker for this type of proteinuria. Once damage occurs, followup studies of workers indicate proteinuria does not decrease even after exposure ends. Thus, renal damage appears irreversible (Piscator 1983). Other signs of renal dysfunction are glucosuria and aminoaciduria, although these usually occur later than proteinuria or following exposure to higher levels of cadmium. An increased incidence of renal stones has also been reported in cadmium workers (Friberg et al. 1974).

Cadmium-induced proteinuria has occurred without detectable morphological changes in the kidneys. However, severe pathological changes do occur with chronic cadmium toxicity. These changes are primarily in the proximal tubules, which can appear grossly atrophied or dilated with the epithelium flattened. There are also changes in the vasculature and ischemic atrophy of glomeruli (Bonnell 1955).

The mechanism of renal tubular damage is believed to be an overload of the detoxification mechanism for cadmium in the kidney (Friberg 1984). As noted in Section V.E, much of the cadmium that accumulates in the kidneys is in the form of cadmium-bound metallothionein, which is freely filtered through the glomerulus and then reabsorbed by the tubular cells like other low molecular weight proteins. Reabsorption via pinocytosis results in cadmium-bound metallothionein accumulation in the lysosomes, where the protein is catabolized and the cadmium ion is released. Free cadmium is normally and rapidly bound to new metallothionein. Toxicity results when the kidneys can no longer produce sufficient metallotheionein to bind excess free cadmium. An early toxic effect is on the reabsorption process of low molecular weight proteins which results in tubular proteinuria. Histopathological changes in the vasculature of affected kidneys may also be due to free cadmium, since cadmium has been found to affect the vasculature in other organs, such as the testes and placenta.

A dose-response relationship for cadmium-induced renal toxicity, has been determined by working backwards from the tissue concentration at which toxicity occurs. This is a reasonable approach since the

biological half-life of cadmium is approximately 10 to 30 years (Friberg et al. 1974).

Several animal studies have shown that morphological changes and/or proteinuria occurred with kidney concentrations of 150 to 225 μg/g wet weight (Kawai et al. 1976, Nomiyama 1975, Suzuki 1975). Friberg et al. (1974) proposed that 200 μg/g wet weight of kidney cortex was the "critical concentration" based on limited human autopsy data. The critical concentration was never explicitly defined but appears to be the average concentration at which an effect was observed. WHO (1977) agreed with this estimate, but gave a range of 100 to 300 μg/g. Nomiyama (1977) suggested that 200 μg/g wet weight is too low of an estimate because Friberg et al. included cases who had morphological changes. Morphological changes could indicate loss of cadmium from the tissue since dead tubule cells containing cadmium would be sloughed off and excreted in the urine. Lower renal cortex cadmium levels were found in cases with pathological changes compared to cases that only had proteinuria.

More recent attempts to correlate renal cortex concentration to renal toxicity have compared the degree of proteinuria to renal cadmium levels determined by the in vivo measurement technique of neutron activation (Roels et al. 1979, 1981, 1983, Ellis et al. 1981). This is a noninvasive method that allows tissue measurements of cadmium in healthy subjects. Unfortunately, there have not been studies comparing this technique to those of conventional analytical techniques (Friberg 1984). However, it was believed by Friberg, Kjellstrøm, and Elinder to

be sufficiently accurate to determine the critical concentration (Kjellstrφm et al. 1984).

Kjellstrφm et al. (1984) evaluated the approaches used by Roels et al. (1981) and Ellis et al. (1981) to estimate the critical concentration, incorporating data generated in these studies to expand the concept of "critical concentration" to include the expected population response rate designated the "population critical concentration" (PCC) (Friberg and Kjellstrφm 1981). The latter is similar in concept to the LD_{50} (lethal dose to fifty percent of a population), so that a critical concentration that is expected to affect 10 percent of a population would be noted as PCC-10. This new concept is more useful than the critical concentration in assessing the risk posed to a population. Kjellstrφm et al. (1984) estimated that the PCC-50 is about 250 to 270 μg Cd/g wet weight of renal cortex and the PCC-10 is about 180 to 220 μg Cd/g wet weight of renal cortex.

Friberg et al. (1974) estimated the necessary daily retention of cadmium to achieve a renal cortex cadmium concentration of 200 μg/g wet weight based on mathematical models that they had developed. Daily retention values were estimated for exposure periods of 10, 25, and 50 years assuming various biological half-lives of cadmium. The assumed half-lives ranged from infinite retention to 9.5 years with a 19 year half-life considered to be most plausible by Friberg et al. . Table VII-1 lists daily cadmium retention values estimated to achieve a renal cortex concentration of 200 μg/g wet weight. Using these values

Friberg et al. (1974) estimated ambient air concentrations necessary to reach the critical concentration in a 10, 25, or 50 year exposure period. Absorption from the lungs was considered to be 25 or 50 percent (See Section V.A). These ambient air concentrations are listed in Table VII-2. For a 50 year exposure period, assuming 50 percent lung absorption and a 19 year biological half-life, the corresponding ambient air level is 1.5 $\mu g/m^3$. Using a similar exposure period and biological half-life, the minimum daily cadmium intake from food or smoking was estimated to be 350 μg/day and 286 cigarettes/day (0.1 μg cadmium per cigarette), respectively. All of these values are independent of each other. Therefore, if ingestion accounted for most of the daily cadmium retention, as expected, exposure to airborne cadmium would have to be reduced to keep the overall daily retention the same. Since the PCC-10 value estimated by Kjellstrøm et al. (1984) is similar to the critical concentration originally proposed by Friberg et al. (1974), the daily cadmium intake values estimated by Friberg et al. may be applicable to the PCC-10 risk level.

Table VII-1

Necessary Daily Cadmium Retention (μg) to Reach Renal Cortex Cadmium Concentration of 200 μg/g (Wet Weight) under Different Excretion Rate and Exposure Time Alternatives

Exposure time in years	Excretion per day, % of body burden (corresponding biological half-time in years in parentheses)				
	0 (∞)	0.002 (95)	0.005 (38)	0.01 (19)	0.02 (9.5)
10	32.9	34.1	35.9	39.2	46.3
25	13.1	14.4	16.4	20.1	28.6
50	6.6	7.8	10.0	14.3	24.6

Source: Friberg et al. 1974, Table 9:2

Table VII-2

Necessary Cadmium Concentration (μg/m³) in Ambient Air to Reach Critical Cadmium Concentration (200 μg/g Wet Weight) in Kidney Cortex under Different Absorption, Excretion, and Exposure Time Alternatives (Ventilation = 20 m³/24 hr)*

Pulmonary absorption (%)	Exposure time in years	Excretion per day, % of body burden (corresponding biological half-time in years in parentheses)				
		0 (∞)	0.002 (95)	0.005 (38)	0.01 (19)	0.02 (9.5)
25	10	6.6	6.8	7.2	7.8	9.3
	25	2.6	2.9	3.3	4.0	5.7
	50	1.3	1.6	2.0	2.9	4.9
50	10	3.3	3.4	3.6	3.9	4.7
	25	1.3	1.5	1.7	2.0	2.9
	50	0.65	0.8	1.0	1.5	2.5

Source: Friberg et al. 1974, Table 9:4

Recently Ellis et al. (1985) reported a study correlating occupational cadmium inhalation exposure to liver and kidney cadmium levels and renal dysfunction. The workers were divided into active and retired categories with normal or abnormal kidney function. Ellis et al. (1985) found a good correlation between the exposure estimates (time-weighted cumulative exposure index) for each worker and liver cadmium levels ($r=0.7$, $p<0.001$). They also found a good correlation between exposure levels and kidney cadmium levels in active workers with normal kidney function ($r=0.83$, $p<0.001$). Active and retired workers with abnormal kidney function tended to have lower kidney cadmium levels, suggesting a loss of cadmium when toxicity occurs. The percentage of workers with abnormal renal function was found to increase with increasing exposure (see Table VII-3). This relationship was examined using linear logistic regression analysis and was found to be best described by the equation:

$$\text{logit } p = 1.24 \ln (TWE) - 8.34$$

where p is the probability a worker would be classified as having kidney dysfunction, logit p is $\ln (p/1-p)$, and TWE is the cumulative exposure index.

Using this relationship, the cumulative exposure index for a probability of classifying 10 percent of the workers as having abnormal kidney function is about 140 $\mu g/m^3$. This would be equivalent to continuous exposure to an ambient air concentration or 2.8 $\mu g/m^3$ for 50 years or 2.0 $\mu g/m^3$ for 70 years. These values are in close agreement with the

value estimated by Friberg et al. (1974). However, they do not take into account exposure from other sources that would be expected to contribute to the cadmium burden in the kidneys.

Table VII-3

Incidence of Abnormal Kidney Function
in Relation to Exposure Category[a]

Time Weighted Exposure Index (yr x $\mu g/m^3$)	Renal Function Classification		Incidence
	Normal	Abnormal	
≤ 20	9	0	0
20 - 100	9	1	0.10
100 - 500	7	2	0.22
500 - 1000	9	6	0.40
1000 - 3000	6	13	0.68
3000 - 6000	1	12	0.92
> 6000	0	7	1.00

[a] Abnormal kidney function was defined as a urinary β_2-microglobulin concentration of > 200 $\mu g/g$ creatinine or total urinary protein > 250 mg/g creatinine.

Source: Ellis et al. (1985), Figure 4.

I. Reproductive Toxicity

Cadmium has been found to cause a variety of adverse reproductive effects, including gonadal toxicity, decreased fertility, placental toxicity, embryo-and fetotoxicity, teratogenicity, and developmental effects. Many of these effects have been extensively studied in experimental animals and looked for in human populations. Numerous recent reviews have been written on the findings of these studies (Barlow and Sullivan 1982, Carmichael et al. 1982, Ferm and Layton 1981, Bhattacharya 1983, EPA 1981). The summary below will give an overview of these findings and only cite studies that give no observed effect levels or other specific information.

1. Gonadal Toxicity

Testicular Damage: It has been well documented that cadmium induces testicular necrosis in experimental animals given an acute dose by intraperitoneal or subcutaneous injection. Pathological changes start to occur within hours of exposure, progressing to edema, hyperemia, hemorrhage, thrombosis and ultimately necrosis of the interstitial tissue and seminiferous tubules. Along with this tissue damage, there is loss of androgen production, which may account for changes in some accessory sex organs such as the prostate. Cadmium may also have a direct effect on the prostate. Variable recovery of the androgen producing tissue does occur; however, there is no regeneration of the seminiferous tubules.

Testicular damage is generally believed to be secondary to cadmium's effect on the capillary endothelium. Capillary damage causes the micro-vasculature to become obstructed, resulting in tissue ischemia. The damage caused by cadmium can be prevented by simultaneous administration of zinc, selenium, cysteine, estrogen, or by pretreatment with non-toxic doses of cadmium. The antagonistic effects of zinc and selenium may be due to an increased intracellular concentration of these metals that prevents cadmium from being incorporated into essential zinc or selenium enzymes. Cadmium incorporation may reduce or abolish these enzyme activities. Pretreatment of small amounts of cadmium probably induces metallothionein synthesis and therefore less free cadmium is available.

Krasovskii et al. (1976) reported that adverse effects in the testicles of rats given cadmium chloride in their drinking water at a dose level of 0.5 and 5 μg/kg but not at 0.05 μg/kg. EPA (1981) states that these reported findings must be viewed with caution because the high control blood levels of cadmium reported are not consistant with the dose levels and because the doses used are less than those likely to be found in food. Dixon et al. (1976) reported that no gonadal effects occurred in rats given drinking water containing 1 to 100 μg/l (maximum dose 14 μg/kg/day) for up to 90 days. Similarly, Loeser and Lorde (1977) reported that no effects occurred in rats fed diets containing 1 to 30 ppm cadmium chloride. Senczuk and Zielinska-Pauja (1977) did report finding damage to spermatogenic tubules and slight interstitial tissue hypertrophy in rats fed diets containing cadmium chloride at 8 or 88 mg/kg diet (ppm) for 12 to 15 months but not when fed the diets

for 3 or 6 months. The extent of damage to the spermatic tubules could not be ascertained nor could the study be evaluated since the information was reported in an abstract.

Ovarian damage: High doses of cadmium chloride, 3 to 10 mg/kg, given by subcutaneous injection have been reported to cause ovarian hemorrhage in mice and rats. Lower doses of 0.22 and 0.45 mg cadmium/kg produced this effect in immature and mature gerbils. Although ovarian follicles in rats underwent mass atresia following injection, upon recovery new follicles differentiated from primordial oocytes and the ovary appeared histologially normal. The effect was found to be inhibited with simultaneous injection of zinc or selenium. Der et al. (1977) reported that daily intramuscular doses of 50 or 250 μg of cadmium chloride for 54 days did not induce any histological change in ovaries of treated rats even though a persistent diestrus was seen in the high dose animals.

2. Fertility

Following cadmium-induced testicular atrophy, there is regeneration of the interstitial tissue. However, there is little or no regeneration of spermatogenesis, so that infertility has been observed in several studies. At a dose, 1 mg/kg by intraperitoneal injection, that caused little or no histopathological effect in the testes, a study in mice indicated that fertility can be reduced, but recovery is possible (Lee and Dixon 1973).

The effect of cadmium on the fertility of females has not been well-studied. Only one study (Sutou et al. 1980) suggested that females given an oral dose of 10 mg/kg/day for three weeks had reduced fertility. Doses of 0.1 and 1 mg/kg/day had no effect. In this study the males were also treated, but, when mated with untreated females, no effect on fertility was observed at any dose level.

3. Placental Toxicity

Cadmium has been shown to induce acute hemorrhagic necrosis of the placenta in laboratory animals given high doses (>1 mg/kg) by systemic injection. Toxicity is believed to be due to cadmium's effect on the vasculature of the placenta, producing ischemia in the tissue similar to the effect found in the testes. Cadmium may also be directly toxic to placental tissue (Di Sant'agnese et al. 1983).

4. Embryo and Fetotoxicity and Teratogenicity

Cadmium is fetotoxic: exposure to levels as low as 8 ppm in the diet or 600 $\mu g/m^3$ in the air throughout pregnancy induced a decrease in body weight and hemoglobin levels of fetal or newborn rats. Following parenteral administration of cadmium at dose levels of around 1 mg/kg, an increase in the percentage of resorptions per litter was observed. Large doses of cadmium produce rapid fetal lethality due to cadmium's placental toxicity.

In addition to causing fetal toxicity, cadmium is also teratogenic. This effect has been observed in an extensive number of studies on a variety of laboratory rodent species, as well as in a few studies on birds, fish, and amphibia. The major abnormalities reported to occur in rodents are cleft palate, limb defects, incompletely developed lung, and CNS defects, such as hydrocephalus and exencephalus.

The dose of cadmium required to induce malformations in rodents has been in the range of 0.6 to 5 mg/kg given parenterally during the period of organogenesis. Ishizu et al. (1973) reported that a subcutaneous injection of 0.63 mg/kg cadmium on day 7 of pregnancy induced a small number of malformations in mice; however, a dose of 0.33 mg/kg did not induce such effects. Nolen et al. (1972a) reported an increase in malformations in rats orally treated with cadmium at 4 mg/kg from days 6 to 14 of gestation, but not when treated at dose levels of 0.01 mg/kg. However, this finding of malformations could not be replicated in a second study (Nolen et al. 1972b).

Cadmium fetotoxic and teratogenic effects have both been found to be antagonized by simultaneous administration of zinc or selenium. Pretreatment with low doses of cadmium have also decreased the fetolethality and teratogenicity of cadmium. This latter effect is probably due to induction of metallothionein, which then detoxifies the later dose of cadmium.

5. Developmental Effects

Animals studies have indicated that developmental effects occur following exposure during gestation, including decreased weight gain, depressed spontaneous activity and other neurobehavioral deficits. One explanation for these effects is that some essential elements, such as zinc, copper and iron, are inhibited from crossing the placenta by cadmium (Carmicheal et al. 1982).

6. Human Reproductive Effects

Few studies have dealt with cadmium's effect on human reproduction. Smith et al. (1960) reported on the histopathology of testes in an autopsy series of five cases with work histories of intermittent occupational exposure to cadmium fumes ending 5 to 19 years before death. The testes were found to be microscopically normal; however, low levels or an absence of spermatids and spermatozoa were observed microscopically. The authors suggested the effects on spermatids and spermatozoa were due to the terminal illness and not cadmium exposure. Favino et al. (1968) reported that one of ten male workers manufacturing nickel-cadmium storage batteries was impotent but no conclusion can be drawn from this anecdotal report.

Tsvethkova (1970) reported that children born to women working in an alkaline battery factory and a zinc molding factory, where cadmium

exposures ranged from 0.1 to 25 mg/m^3 and 0.02 to 25 mg/m^3, respectively, had significantly lower birth weights than an unexposed control group. Four of 27 children born to women working in the zinc molding factory were reported to be born with clear signs of rickets. The details provided in the study are not sufficient to evaluate these results (Barlow and Sullivan 1982).

7. Conclusion

Animal studies have shown that cadmium can have multiple effects on reproduction. It is toxic to the gonads and placenta and can cause fetotoxicity and teratogenicity. Adequate human evidence of reproductive toxicity is lacking and a no-observed-effect-level (NOEL) cannot be estimated from human data. Animal data would suggest the NOEL to be no greater than 100 μg/kg/day. This would be equivalent to an airborne concentration of about 330 μg/m^3. Even when safety factors are included to take into account population and species variability, and exposure duration, the ambient exposure level is below what might reasonably be considered a safe exposure level for reproductive toxicity.

J. Carcinogenic Effects

1. Mutagenicity

The mutagenic potential of cadmium has been examined using a variety of methods and test systems. Prokaryotic systems have been used to assess

gene mutation and reparable genetic damage caused by cadmium. Gene mutation has also been studied in yeast, Drosophila, and mammalian cells. In vitro and in vivo work has been done to assess the role of cadmium in inducing chromosomal aberrations in mammalian systems including humans. Many of these studies have recently been reviewed and evaluated by EPA (1985). The following discussion summarizes the general findings from these studies.

Using Salmonella typhimurium tester strains, several studies have indicated that inorganic cadmium salts do not induce gene mutations. A positive response was observed in one study where cadmium diethylthiocarbamate was tested (Hendenstedt et al. 1979). This effect occurred at only one of the intermediate concentrations used, so no dose-response relationship was observed. However the effect occur at that concentration in two different tester strains. Zinc diethylthiocarbamate was also mutagenic in this study, suggesting that diethylthiocarbamate and not cadmium was the mutagenic moiety. The results of two studies using the Bacillus subtillis rec-assay indicate that cadmium in soluble inorganic salts is weakly mutagenic in that system (Nishioka 1975, Kanematsu et al. 1980). Cadmium was also found to act synergistically with a potent mutagen, N-methyl-N-nitro-N-nitrosoguanidine, in the S. typhimurium test system (Mandel and Ryser 1981).

Cadmium chloride was reported to produce a positive mutagenic response in the yeast Saccharomyces cerevisiae (Takahashi 1972). However, this effect was weak and did not follow a dose-response relationship. In

addition, one endpoint, petite mutations, involve mitochondrial DNA and not nuclear DNA.

Positive mutagenic responses have been reported for cadmium chloride and cadmium sulfate when tested in the mouse lymphoma L5178YTK+/- assay system. This effect occurred in a dose-related manner at cadmium concentrations between 10^{-7} and 10^{-6}M (Oberly et al. 1982). Other mammalian cell test systems have also been reported to show weakly positive mutagenic activity when soluble cadmium salts were used.

A number of studies have been conducted with Drosophila melanogaster as the test organism, using different endpoints to test cadmium mutagenicity. Most test results were considered negative (Sorsa and Pfeifer 1973, Sabalina 1968, Ramel and Magrusson 1979, Inone and Watanabe 1978). The results reported for one study, however, indicated that cadmium chloride induced an increased frequency of dominant lethal mutations (Vasudev and Krishnamurthy 1979).

Cadmium's ability to induce chromosomal aberrations has been studied in in vitro systems using human cells and other mammalian cell lines with mixed results. Cadmium sulfide was reported to have induced a large number of chromosomal aberrations in human lymphocytes in one study (Shiraishi et al. 1972). This study has been criticized because the cells came from only one donor, only one concentration of cadmium was used, the solvent used for the insoluble cadmium compound was not stated, and only a limited number of cells were examined. A second study was also reported to have been positive using human lymphocytes

exposed to cadmium acetate over a concentration range of 4 orders of magnitute (Gasiorek and Barichinger 1981). Although there was a dose-related increase in chromosomal gaps, the increase in structural aberrations was not dose-related. Other studies with human lymphocytes using similar concentrations were reported to be negative.

Soluble cadmium salts have been reported to induce chromosomal aberrations in other cultured mammalian cells at concentrations similar to the ones that caused this effect in human lymphocytes. Rohr and Bauchenger (1976) found that cadmium sulfate induced numerical chromosomal aberrations in the Chinese hamsters cell line "Hy" by interfering with spindle function. Cadmium chloride induced chromosomal aberrations in cultered Chinese hamster ovary cells when grown in the presence of bovine serum but not when the bovine serum in the media was replaced by fetal calf serum (Deaven and Campbell 1980). This suggests the culture media used can influence the outcome of a study.

As in the other test systems, results from in vivo animals studies on cadmium mutagenicity and clastogenicity have been mixed. Several mutagenicity studies looking for dominant lethal effects in rats gave negative results. However, dominant lethal assays are relatively insensitive for detecting all types of mutagens (Russel and Matter 1980). On the other hand, several studies showed that cadmium treatment induced nondisjunction in oocytes and blastocytes of experimental animals. Cadmium chloride did not induce chromosomal aberrations nor

increase the frequency of micronuclei in bone marrow cells of treated mice.

A number of studies have examined whether occupational or environmental exposure to cadmium increased the number of chromosomal aberrations found in human blood lymphocytes. Two out of six studies reviewed by EPA (1985) reported significant increases. One of the positive studies had been on Itai-Itai patients, but a negative study was also reported in Itai-Itai patients (Shiraishi 1975, Bui et al. 1975). Patients from the negative study had not been given drugs or x-rays while the cohort of the positive study was not controlled for these factors, which can seriously influence the results of this type of study. The cohort from the other positive study had been occupationally exposed to cadmium and other metals. These other metals may also have had an effect.

Although not all genotoxicity studies on cadmium were positive, the results of several studies on mammalian and bacterial gene mutation and chromosomal aberrations in-cultured mammalian cells and intact animals that suggest that cadmium is mutagenic. However, a definitive conclusion cannot be made until the bases for discrepancies in results of similar studies are better understood.

In summary, bacterial test systems have given conflicting results. Inorganic cadmium salts failed to induce reverse mutations in Salmonella typhimurium tester strains used in an Ames assay system; however, they were found to be weakly mutagenic to Bacillus subtilis strains used in the rec-assay system. The discrepancy could be from

species or assay system differences. Soluble cadmium salts were weakly mutagenic in a number of studies using mammalian cells. Although the high concentration of cadmium proved to be toxic in some studies, positive findings were obtained when cell survival was considered adequate. Only one of a number of mutagenicity studies using Drosophila melanogaster reported positive findings. In vivo animal mutation studies have been negative, but these studies are relatively insensitive.

Mixed results were found in studies that examined cadmium's ability to induce chromosomal aberrations in cultured animal and human cells. One study indicated that cadmium may cause some aberrations by interfering with spindle function. Results of another study suggest that culturing conditions could significantly affect the results and thus make it difficult to draw any conclusions from these in vitro studies on chromosomal aberrations. In vivo animal studies have produced mixed results. The positive findings indicated that cadmium affected spindle function. These findings in vivo correlate with the findings of one in vitro study. Although an increase in chromosomal aberrations has been found in two studies on lymphocytes taken from exposed humans, confounding factors may have affected the validity of these results.

The information reviewed suggests that cadmium may induce mutations and chromosomal aberrations. However, this evidence is limited and in a number of cases there are conflicting results. Therefore, at this time the staff of DHS regards the evidence of genotoxicity as suggestive but inconclusive.

2. Carcinogenicity

Animal Studies

Cadmium has been the subject of numerous studies in experimental animals to determine its carcinogenic potential. Many of these studies involved subcutaneous or intramuscular injection, others oral administration, and several recent studies have involved intratracheal injection or inhalation of an aerosol. These studies have been extensively reviewed elsewhere (IARC 1973, 1976; EPA 1981, 1985; Sunderman 1977) and for the most part will only be briefly discussed here.

Injection Studies

Most studies in which rats were given subcutaneous or intramuscular injections of a cadmium compound found that injection site tumors formed. The cadmium compounds used were primarily soluble inorganic cadmium salts, but insoluble cadmium salts and cadmium metal powder were also effective in inducing tumors. The tumors that were formed were sarcomas, which are the most common type of injection site tumor. Induction of injection site sarcomas can indicate a compound is carcinogenic, but the studies are not useful for quantitative evaluation of the compounds carcinogenic potential because of the atypical route of exposure. The vast majority of injection route studies have been in rats and only a small number of mouse studies have been reported. Injection site tumors have not been seen in the few studies conducted with mice.

Although injection site tumors were not found in mice, in one study a high incidence of interstitial-cell tumors of the testis was found in treated mice, while no such tumors were found in control animals (Gunn et al. 1963). Tumors formation followed cadmium-induced testicular damage and tissue regeneration. Similar findings of a high incidence of interstitial-cell testicular tumors were also reported to have occurred in a number of rat studies (Gunn et al. 1964; Levy et al. 1973; Poirier et al. 1983). In a recent study (Poirier et al 1983), rats given a subcutaneous injection of cadmium chloride were found to have a significantly increased incidence of pancreatic islet cell tumors (3 of 137 control, 22 of 259 treated; $p<0.02$). This is of interest because the pancreas is one of the tissues found to accumulate cadmium.

In two studies Gunn et al. (1963,1964) injected rats with zinc acetate at the same site as cadmium chloride but at 100 times the dose. They found that zinc decreased the incidence of local and interstitial cell testicular tumors. Poirier et al. (1983) found that magnesium acetate injected at the same site as cadmium chloride at 300 to 600 times the dose inhibited formation of local tumors but did not have a noticeable effect on the induction of testicular tumors.

Oral Administration

Several of chronic studies have been conducted in which soluble cadmium salts were administerd to mice or rats via their drinking water or diet or by gavage. None of these studies indicated that cadmium was

carcinogenic. The most adequate studies conducted include those done by Levy and Clack (1975) and Levy et al. (1975) who examined the carcinogenicity of cadmium sulfate in rats and mice, respectively. Groups of 50 male rats were given weekly oral doses of 0.087, 0.18, or 0.35 mg cadmium sulfate/kg for a two year period. No increase in tumor incidence was observe. Groups of 50 male mice were given weekly oral doses of 0.44, 0.88, or 1.75 mg cadmium sulfate/kg. No increase in tumor incidence compared to the control group was observed in this study. The primary objective of these studies was to investigate prostate cancer and therefore the number of tissues examined was limited. In addition the rat strain used has a normal high lifetime incidence of spontaneous interstitial cell tumors which makes it very difficult to observe an increase in this type of tumor.

EPA (1985) evaluated an unpublished FDA (1977) study. Groups of 26 to 32 male and 26 to 29 female Charles River rats were given diets containing 0, 0.6, 6, 30, 60, 90 ppm cadmium chloride for 103 weeks. No increase incidence of any tumor was found. These levels of cadmium did not have an effect on survival, although electron microscopy revealed some changes in the kidneys.

Loeser (1980) also conducted a two year carcinogenic bioassay in rats. Groups of 50 male and 50 female Wistar rats were given cadmium chloride in their diets at concentration of 0, 1, 3, 10, or 50 ppm cadmium. The only statistically significant effect was a reduction in body weight of the high dose male group.

Inhalation and Intratracheal Administration

Sanders and Mahaffey (1984) examined the carcinogenic potential of cadmium oxide in male rats by intratracheal instillation. The rats were treated one, two or three times with 25 μg of cadmium oxide. The first administration was given at 70 days of age and then at 100 and 130 days of age depending on the total dose to be given. i.e. 25, 50, or 75 μg. The animals were then followed for their lifetime. No differences were found in survival times or organ weights between treated and control groups. Using life-table and contingency table statistical analyses a significant increase in benign mammary fibroadenomas was observed in the high dose group. Additionally, there was a significant increase in the number of rats in the high dose group that had three or more tumor types.

Hadley et al. (1979) exposed a group of 61 male Wistar strain rats one time to an airborne cadmium oxide aerosol concentration of 60 mg/m^3 for 30 minutes. The mass median diameter of the particles was 1.4 μm with a geometric standard deviation of 1.9 μm. Seventeen animals were used as controls. Twenty-seven exposed animals died within three days from acute pulmonary edema. The remaining animals were then observed for one year. No morphological changes were noted in the lungs of exposed animals, although one animal did have a well-differentiated pulmonary adenocarcinoma. The authors observed that this tumor's relatively short latency period and the low spontaneous incidence (0.1%) of such tumors suggested that it resulted from cadmium exposure.

Both the Sander and Mahaffey (1984) study and the Hadley et al. (1979) study are not adequate to assess carcinogenic potency, since the animals were only exposed for short periods and, in the Hadley et al. (1979) study, were not followed for sufficient time. Without continuous exposure, effects in the lungs may not occur or the study may not be sensitive enough to detect adverse effects.

In the only long-term inhalation study, Takenaka et al. (1983) exposed rats to several concentration of a cadmium chloride aerosol. Groups of 40 male Wistar rats were exposed to a continuous (23.5 hours/day) airborne concentration of 13.4, 25.7, or 50.8 μg of cadmium/m^3 of air for 18 months. A control group of 41 rats was exposed to filtered room air. The aerodynamic mass median diameter of the aerosol particles was 0.55 μm with a arithmetic standard deviation of 0.48 μm and a geometric standard deviation of 1.8 μm. The rats were followed for an additional 13 months before surviving rats were sacrificed.

There were no statistically significant differences seen in body weight or survival between exposed and control groups. The incidence of lung carcinomas was significantly increased ($p > 0.014$, Fisher's Exact Test) in all exposure groups. Three lung tumor types were identified, adenocarcinoma, epidermoid carcinoma, and mucoepidermoid carcinoma. The numbers of animals in each group that had these tumors types are given in Table VII-4. The first lung tumor was observed at 20 months. In the high-dose group, the first tumors were observed at 23 months and 23 out of 25 animals in this group dying or sacrificed after 27 months had lung tumors. Thus, these appear to be late-developing tumors.

Table VII-4

Lung Tumors in Rats Exposed to
Cadmium Chloride Aerosols

Exposure Group[a]	No. of Rats Examined Histologically	No. of Rats with Tumors			
		Adenocarcinoma	Epidermoid Carcinoma	Mucoepidermoid Carcinoma	Total Carcinomas
Control	38	0	0	0	0
13.4μg/m^3	39	4	2	0	6
25.7μg/m^3	38	16	5	0	20[b]
50.8μg/m^3	35	15	8	3	25[b]

[a] Airborne exposure concentrations are based on the cadmium, not cadmium chloride, concentration.

[b] One rat had both an adenocarcinoma and an epidermoid carcinoma.

Source: Takenaka et al. 1983.

This observation suggests the need for studies of long duration in order to detect increased tumor incidence from exposure to other cadmium compounds.

Summary

Injection and inhalation exposures to cadmium have caused increases in the incidence of neoplasms. No study, in which cadmium has been administered by the oral route, has shown such exposure to induce neoplasms. The most likely explanations for this discrepancy are that limited gastrointestinal absorption reduces the systemically absorbed cadmium to levels that were too low for the statistical power of the studies to detect a carcinogenic response and the gastrointestinal tract epithelical tissue is not a sensitive tissue for cadmium induced carcinogenicity.

Human Studies

The EPA has produced a detailed and up-to-date review of the epidemiologic evidence on health effects due to cadmium exposure (EPA 1985). Staff members of DHS have summarized the most important and/or current studies in Table VII-5. Most of the studies were occupational mortality studies in which cause-specific death rates were compared to expected rates based on a standard population; the ratio of observed to expected yielding a standardized mortality ratio (SMR). The studies by Thun et al. (1985) and Varner et al. (1983) are both follow-up studies of the cohort examined by Lemen et al. (1976). The study by Armstrong

and Kazantzis (1983) combined men from 17 plants in which a potential for cadmium exposure is present. Two studies focused on prostate cancer incidence rather than mortality: a cohort study in an occupational setting (Sorahan and Waterhouse, 1985); and a case-control study from a population-based tumor registry (Ross et al. 1983). Inskip et al (1982) conducted an historical cohort SMR study on the populations of two towns, one with and the other without high soil cadmium content. A case-control study of renal cancer examined cadmium exposure via several routes (Kolonel 1976).

Outcomes examined in these investigations included cancer of the respiratory tract, prostate, bladder, kidney, and gastrointestinal tract; nonmalignant causes of death included: gastrointestinal disease, respiratory disease, nephritis and nephrosis, cerebrovascular disease, and hypertension. The results are not entirely consistent, but the evidence for an effect of cadmium exposure is strongest for lung cancer, prostate cancer, renal cancer, and nephritis and nephrosis. Discussions of carcinogenic effects are presented below in three sections:

(a) Genitourinary Cancer

(b) Respiratory Cancer: Overview

(c) Respiratory Cancer: Study by Thun et al.

Table VII-5

Summary of Salient Epidemiologic Studies on Carcinogenicity of Inhaled Cadmium

AUTHOR & DATE	STUDY DESIGN	METHOD OF ANALYSIS	N	OUTCOMES	RESULTS	NOTES	HOW EXPOSURE ASSESSED
Lemen et al. 1976	Occup SMR Cohort consists of all workers exposed to cadmium and employed for > 2 years	SMR	292	All cancer Resp Ca Prostate Ca	+ + (+)	(+) significant only when analysis assumed a 20-year minimum latency period	No quantification
Thun et al. 1985	Occup SMR [followup of Lemen et al. but expanded cohort]	SMR	602	All cancer Resp Ca Prostate Ca Genito-urinary Ca Nonmalign GI dis Nonmalign resp dis	- + - - + -	Strong dose-response, unlikely to be due to confounders. Authors suggest nonfatal cases may be in excess, but no new deaths since study by Lemen et al.	Cumulative mg-days/m^3 using industrial hygiene surveys since 1943 and personal monitor measurements in 1973-1976.
Varner 1983	Occup PMR [followup of Lemen et al; expanded cohort differs from Thun by including nonwhites, nonmales, and guards and janitors]	PMR	585	All Ca Lung Ca Urinary organ Ca Bladder Ca Ulcer of stomach and duodenum Nonmalign resp dis	+ + + + + +	Dose response, potential for some confounding due to smoking $p < .01$ $p < .01$	Same as Thun et al. but in cumulative mg-years/m^3
Andersson et al. 1984	Occup SMR All men were also exposed to nickel, a recognized carcinogen.	SMR	525	All Cancer Nephritis and nephrosis Lung Ca Prostate Ca Bladder Ca Obstructive lung dis	- + - (-) (-) (-)	Significant in those with at least 15 years exposure Smoking habits among those alive in 1981 were similar to those of Sweden as a whole (-) "possibly" elevated though not statistically significant	Duration of employment. Authors acknowledge deficiency in this measure due to sharp decline in Cd levels over time.

AUTHOR & DATE	STUDY DESIGN	METHOD OF ANALYSIS	N	OUTCOMES	RESULTS	NOTES	HOW EXPOSURE ASSESSED
orahan & aterhouse 1983	Occup SMR	SMR	3025	All Ca	-		No quantification for SMR
				Prostate Ca	-		
	[followup of report by			Resp Ca	+		
	Kipling and Waterhouse 1967, not shown in this table]	RMLT	2912	Prostate Ca	(+)	No longer positive if initial cases of earlier study are excluded.	For RMLT Cumulative years of employment in (1) high or (2)high or moderate exposure job.
				Resp Ca	+	Positive for those with length of followup ≥ 30 years	
	Cohort consists of all potentially exposed workers.			Nonmalign resp dis	-		
orahan & aterhouse 1985	Occup incidence [further followup of 1983 report by same authors]	SIR	2559	Prostate Ca incidence	(±)	Exclusion of 4 index cases yields nonsignificant result, while inclusion of the original 4 yields p = .001	No quantitative assessment All workers in factory were considered exposed if employed > 1 month.
						Cases based on Birmingham Regional Cancer Registry. Completeness of that registry's ascertainment was not discussed	
rmstrong & azantzis 1983	Occup SMR	SMR	6995	Prostate Ca	-		Each job was categorized as high, med, or low exposure. The workers were classified as "ever high," (3%) "ever medium," (17%) or "always low" (80%)
	Combined men from 17 major plants involved in processes using cadmium These workers were therefore exposed to different forms of cadmium, eg dusts, oxide fumes, etc. They were also heterogeneous with respect to other chemical exposures.			Lung Ca	(+)	SMR significant at p<.05 for workers with >10 years "always low" exposure. Other categories had low power.	
				Cerebrovascular dis	-		
				Hypertensive dis	-		
				Bronchitis	+	Highly significant for the small group with "ever high" exposure	

AUTHOR & DATE	STUDY DESIGN	METHOD OF ANALYSIS	N	OUTCOMES	RESULTS	NOTES	HOW EXPOSURE ASSESSED
Kolonel 1976	Case-control: 2 sets of controls -colon cancer -nonmalign digestive disease	Stratified RR	64 cases 72 colon cancer 197 non-cancer controls	Renal Ca	+	Disease group of noncancer controls was found by Thun et al. to have elevated mortality assoc with Cd exposure. This may strengthen the results. Renal cancer may be too rare to be detected in SMR studies.	Occ: high risk job in high risk industry(yes/no). Cd in tobacco: lifetime pack years - surrogate quantification. Cd in diet: dietary history used to establish unusually high Cd dietary intake.
Ross, Paganini-Hill & Henderson 1983	Case Control study of prostate cancer incidence	Matched pair OR, also PIR for prostate vs other cancer	110 pairs	Prostate Ca	(-)	$p > .05$, but OR = 2 for job exposure to Cd	Employment in an occupation with possible Cd exposure, occupational history from interview
Inskip, Beral & McDowall 1982	Historical cohort of two towns, Shipham with high soil Cd content; Hutton with none	SMR however a direct comparison of rates in the two towns was not performed	911 for both towns	Respiratory dis GI Ca Lung Ca Prostate Ca Genito-urinary dis (inc: nephritis & nephrosis) Hypertensive dis Cerebrovascular dis	- - - - (+) (-) +	SMR significant at $p < .10$ for males SMR not significant but RR > 2 when comparing Shipham to Hutton residents: males, females, or sexes combined SMR significant at $p < .05$ for females or both sexes.	1979 soil samples were used to assign GI tract exposure levels to 70% of Shipham residents; homegrown food was considered main source. Assumed those exposures applied in 1939.

Abbreviations: N = number in cohort, Cd = Cadmium
SMR= Standardized mortality ratio, PMR = Proportional mortality ratio, PIR = Proportional incidence ratio,
RMLT = Regression method of life tables, SIR = Standardized incidence ratio, RR = Relative risk, OR = Odds ratio
+ indicates a statistically significant positive association with $p \leq .05$

Genitourinary Cancer

Noncarcinogenic effects of cadmium on kidney function have been well documentd (See Section VII.H), however, the rarity of renal cancer renders prospective studies impractical for detecting an increase in neoplasms at this site. A case-control study of renal cancer among an occupationally exposed population utilized two control groups: (i) colon cancer cases (as a means of equalizing proclivity for recall of previous exposure), and (ii) nonmalignant digestive disease cases (Kolonel 1976). The renal cancer cases were characterized by a greater odds of having worked in a job with a high risk of cadmium exposure than either control group. Later findings by Thun et al. 1985, Varner 1983 showed that nonmalignant digestive disease may also be associated with cadmium exposure. Since any association between the disease of the control group and cadmium will tend to mask the effect on renal cancer, the positive finding by Kolonel is more convincing. In addition, a review of death certificates by Andersson et al. (1984) disclosed a case of renal cancer, which the authors believed was due to 30 years of cadmium exposure. Staff members of DHS conclude that the evidence is insufficient to infer causation, but is suggestive of an association between cadmium exposure and renal cancer.

The case for an association with prostatic cancer remains inconclusive. Table VII-6 summarizes the epidemiologic evidence for such an association. Lemen et al. (1976) found an excess of prostate cancer deaths among 292 workers employed for greater than two years in a job

with potential cadmium exposure. The excess was significant if the analysis assumed a 20-year latency period. However, a follow-up study of this cohort by Thun et al. (1985) uncovered no new deaths due to prostatic cancer. The authors suggested that given the generally nonfatal nature of the disease, mortality studies frequently may not be sensitive enough to detect a potentially real association with incidence of prostate cancer. Sorahan and Waterhouse (1983, 1985) followed up a 1967 report by Kipling and Waterhouse which had found a highly significant excess incidence of prostatic cancer. Both the incidence report (Sorahan & Waterhouse, 1985) and the mortality study (Sorahan & Waterhouse, 1983) found no significantly elevated risk if the original four index cases were excluded. However, inclusion of these cases in the analysis yielded a highly significant association. For mortality, using cumulative years of high exposure to cadmium, the p-value was less than .05 when controlling for sex, year of study, employment, age at starting employment, and duration of employment. For morbidity, using more than one year of high exposure, $p<0.001$ (1.99 expected, 8 observed, p-value not given by authors but calculated by DHS staff based on a Poisson distribution). Tumor incidence was determined using the Birmingham Regional Cancer Registry. The authors do not provide information on completeness of ascertainment by this registry.

The SMR study by Andersson et al. (1984) and the matched case-control study by Ross et al. (1983) both failed to reject the null hypothesis of no effect on risk of prostate cancer. However, the SMR was considered "possibly" increased and the lack of statistical

Table VII-6

Association Between Cadmium Exposure
and Prostate Cancer Deaths

Authors	Magnitude of Association	Significant at p<.05
Sorahan & Waterhouse 1983	SMR=121 excluding 4 index cases	N[a]
Armstrong & Kazantzis 1983	SMR=99 for entire cohort	N
Andersson et al. 1984	SMR=129 for entire cohort =188 for those with >15 years exposure	N
Inskip et al. 1982	SMR=121	N
Lemen et al. 1976	SMR=348 for all workers =452 for those with >20 years followup	N Y
Ross et al. 1983	OR=2.0	N
Thun et al. 1985	SMR=213 for those with >20 years followup and >2 years exposure	N
Varner 1984	PMR=169	N

[a] Y if 4 index cases are included

significance could have been due to deficiencies in the measure of exposure. Similarly in the study by Ross et al., the odds ratio (OR) for cadmium exposure among prostatic cancer cases as compared to controls was 2. The smallest OR which would have an 80% chance of being detected as statistically significant in a study this size is 4, thus the lack of significance should be interpreted cautiously.

Calculations of the statistical power for detecting relative risks of 1.25, 1.5 and 2.0 for "negative" studies of prostate (and respiratory) cancer mortality are shown in Table VII-7. It is clear that, in general, the power of these studies was not sufficient to detect the small relative risks for prostate cancer deaths expected from cadmium exposure.

The evidence appears to be inconclusive regarding the effect of cadmium exposure on prostatic cancer. Given the highly significant early reports, it may be that cadmium acts as a promoting agent, inducing earlier tumors in those already susceptible. This effect may have been reduced markedly in recent years due to the lowering of exposure levels, sometimes by an order of magnitude or more (Thun et al. 1985, Andersson et al. 1984, Sorahan and Waterhouse 1985). Thus, those with earlier exposure may have been at highest risk, and the cohorts most recently studied, being heterogeneous with respect to their exposures, show only nonsignificant increases in prostate cancer incidence, e.g., a doubling or less, and no increase in mortality.

Table VII-7

Power to Detect an Elevated SMR at $\alpha = 0.05$

	If true SMR is:		
	125	150	200
1. Prostate Cancer			
Thun et al. 1985	0.06	0.12	0.28
Andersson et al. 1984	0.10	0.19	0.43
Sorahan & Waterhouse 1983	0.13	0.29	0.67
Inskip et al. 1982	0.04	0.08	0.21
2. Respiratory Cancer			
Andersson et al. 1984	0.10	0.22	0.54

Because the human studies repeatedly find some elevation in risk, albeit a nonsignificant one, the staff of DHS does not believe that the is evidence is conclusive to reject an effect of cadmium on prostate cancer.

The PMR analysis by Varner (1983) showed the proportion of bladder cancer deaths to be in excess of what would be expected in the standard US population. The occupational SMR study by Andersson et al. (1984) showed a nonsignificantly elevated risk of bladder cancer deaths. The data are too scant to be conclusive regarding the effect of cadmium exposure on bladder cancer.

Respiratory Cancer: Overview

Table VII-8 summarizes the epidemiologic evidence relating respiratory cancer SMR's to cadmium exposure. A significantly increased risk of respiratory cancer deaths was seen by Lemen et al. (1976), Thun et al. (1985), Sorahan and Waterhouse (1983), Varner (1983), and Armstrong and Kazantzis (1983), but not by Inskip et al. (1982) nor by Andersson et al. (1984). However, the assessment of exposure in the two towns investigated by Inskip et al. relied only on 1979 soil samples for exposure from 1939 to 1979. Even with a questionable exposure assessment, males in the exposed town had a lung cancer SMR which, while not statistically significant, was nearly double that of males in the unexposed town (101 vs 55). The other negative study (Andersson et

Table VII-8

Association Between Cadmium Exposure
and Respiratory Cancer Mortality

Authors	SMR	Significant at p<.05
Sorahan & Waterhouse 1983	127	Y
Lemen et al. 1976	235	Y
Thun et al. 1985	229	Y
Armstrong & Kazantzis 1983	126[a]	Y
Inskip et al. 1982	101[b]	N
Andersson et al. 1984	120	N

[a] For workers with >10 years exposure in the "always low" category (the number of workers with "ever medium" and "ever high" exposures was small).

[b] vs. SMR=55 for the unexposed town.

al.) had low statistical power to detect a SMR of less than 200 (see Table VII-7). In other studies, the range of SMR's for respiratory cancer was 120-230 (see Table VII-8). The staff of DHS concluded thatthe two negative studies for respiratory cancer are not convincing evidence of no effect, due to low statistical power in one study and poor exposure data in the other.

The study by Thun et al. (1985) showed a positive dose-response relationship where dose was expressed as cumulative mg-days/m^3. Varner (1983) reported the lung cancer PMR (proportional mortality ratio) to be elevated (see Table VII-5 for description of how this cohort differs from that of Thun et al.). Sorahan and Waterhouse (1983), in two separate analyses, found an elevated risk of respiratory cancer. The first analysis was based on the SMR and included all potentially exposed workers. The second analysis used the regression method of life tables (RMLT) and assessed exposure by cumulative years employed in a (1) high exposure job or (2) high or moderate exposure job or (3) high or moderate exposure job excluding welding. Measures (2) and (3) resulted in a significant effect of exposure on respiratory cancer, particularly for those with more than 30 years of follow-up.

In epidemiologic studies, the potential for confounding due to extraneous risk factors requires attention. If a cadmium-exposed cohort smoked excessively, or experienced exposures to other carcinogens, such as nickel or arsenic, then the apparent association between cadmium and respiratory cancer, for instance, could be at least partially explained by these factors.

Heavier smoking among cadmium workers as compared to the general population could account for the small but statistically significant SMR for lung cancer (126) observed by Armstrong and Kazantzis for those exposed >10 years at the "always low" catagory. No smoking histories were available. Sorahan and Waterhouse also lacked data on smoking, but they argue that smoking was unlikely to have been a confounder for two reasons. First, their analysis showed an increasing association with duration of employment, while smoking habits are unlikely to be well-correlated with duration of employment. Secondly, deaths from other diseases of the respiratory system were not elevated, as they would have been if the cohort had included a disproportionate number of smokers. However, the effect of nickel hydroxide could not be disentangled from that of cadmium oxide in this cohort.

The strongest evidence for cadmium-induced carcinogenicity in humans is the study conducted by Thun et al. The characteristics of this study which make it particularly convincing are the quality of the exposure data and the analysis of potential confounding. Since the quantitative results of this study constituted the basis for the DHS risk assessment of cadmium, a full description of this study is presented below.

While some of the observed association between lung cancer and cadmium may be explained by confounding factors, the consistency of results for several cohorts and several types of analyses, the dose-response pattern seen in the one study with quantitative exposure data, the finding in some studies that other smoking-related causes of death were not

elevated, and the magnitude of effect observed, suggest that confounding cannot explain all of the association.

The evidence from epidemiology strongly supports the hypothesis that cadmium exposure is associated with an increased risk of respiratory cancer. Since this site has also been implicated in animal bioassays of carcinogenicity, DHS staff members concluded that there is a high probability that the observed association is not spurious and that an inference of causality is justified.

Respiratory Cancer : Study by Thun et al.

Thun et al. conducted a follow-up of the report by Lemen et al. (1976), who had found an increase in mortality from respiratory and prostate cancer and from nonmalignant lung disease in a cohort of cadmium smelter workers. Thun et al. expanded the cohort and extended the follow-up period. The final cohort included those hired after 1925 and employed 6 months or longer in production areas of the plant during the period 1940-1969. The cause-specific death rates were adjusted by the indirect method to yield standardized mortality ratios (SMRs) and by the direct method to yield standardized rate ratios (SRRs). The SMR for lung cancer in the overall cohort was 147, while for those with 2 or more years of employment it was 229, with a 95% confidence interval of (131,371).

Exposure data that had been collected since the 1940's allowed evaluation of the lung cancer SMR by dose. Industrial hygiene measurements for departments and job sites with potential cadmium exposure were available (Smith et al. 1980). These were combined with individual work histories for each member of the cohort in order to assign an exposure level to each work day. Interruptions of employment were taken into account and exposure levels were adjusted to reflect respirator usage in departments where these were worn. A cumulative exposure in mg-years/m^3 was then assigned to each person-year of follow-up for each worker. The range of cumulative exposures was divided into three categories, and both SMRs and SRRs were calculated for each category. The results are shown in Table VII-9 using US white males as the comparison population, and in Table VII-10 using Colorado white males as the comparison population. (Thun presented the analysis using Colorado white males as the control group at the Fifth International Cadmium Conference February 1986, in San Francisco. This analysis assumes that pre-1950 lung cancer rates equaled those in 1950, since cause-specific rates were not tabulated in that state before 1950.)

The data indicate a clear dose-response relationship between cumulative cadmium exposure and the risk of death due to lung cancer. Using the US population as the comparison group, both the SMR and the SRR rise from about 1/2 the expected at "low" cumulative exposure to about 3 times the expected at high cumulative exposure. Both of these measures of risk are larger when the Colorado population is used as a standard, with the SRR rising from 0.7 to over 5.0.

The strength of evidence of causality provided by any single study depends on the degree to which one can rule out alternative explanations of the observed effect. Alternative explanations fall into 3 categories. (1) chance, (2) bias, (3) confounding. The study by Thun et al. is examined below in this context.

Chance

Thun et al. calculated the standardized rate ratio (SRR) for each of 3 exposure groups. (The person-years at risk, rather than individual workers, were classified by cumulative exposure to that point in time.) The SRR is suitable for subgroup comparisons, but not for external comparisons. A regression of the SRRs yielded a slope of 7.33×10^{-7}, which differed from zero with a probability of .0001. In other words, the probability that the increase in lung cancer risk associated with increasing exposure to cadmium was due to chance was about one in ten thousand.

Bias

Selection criteria described by Thun et al. appear to have been unbiased: all retired, deceased, and active employees who had worked a minimum of 6 months in production areas of the plant were included in the cohort. In calculating cumulative exposure, dates of interruption of employment were accounted for. Since more than 80% of the workers were followed for 20 or more years it is likely that the follow-up was sufficient for many latent cadmium-induced cancers to become manifest

and lead to death. Trained nosologists evaluated the death certificates. As indicated by Thun et al., one lung cancer death was originally miscoded as being due to another cause. Removal of this death from the lung cancer deaths (i.e. restoring it to the original, but incorrect coding) is necessary in order that the comparison with general population rates be unbiased (since miscodings also occur in the general population). However, the findings are not altered in any substantial way by this reclassification.

Exposure categories were chosen prior to the analysis. The cumulative exposure for all person-years was miscalculated by Thun et al. because they included non-workdays. This does not cause bias for purposes of inference since the misclassification was equivalent for all exposure categories. It would, however, alter the dose-response relationship, and therefore DHS staff adjusted for this error in conducting our risk assessment, since an overestimate of exposure would result in an underestimation of potency. The corrected exposures are shown in Tables VII-9 and VII-10. (See also Table IX-3.)

Confounding

If the cadmium-exposed workers included a disproportionate number of individuals with exposures to other agents responsible for lung cancer, then the observed association might be spurious. The potential confounders with regard to lung cancer mortality in this cohort were smoking and arsenic exposure.

(a) Smoking:

Indirect evidence that smoking was not a confounder in this cohort is provided by the cardiovascular death rate in this cohort, which was 35% lower than expected based on U.S. white male death rates. If this cohort included a higher proportion of total smokers or heavy smokers as compared to the general population of white males in the same age categories, then one would expect an increase (or at least not a deficit) in the cardiovascular death rate as well.

Data on the smoking habits of these workers were provided to Thun et al. by the company. The data came from company medical records and from a questionnaire survey mailed to surviving workers or the next-of-kin in 1982. The results of this survey have elicited differing interpretations depending on the choice of measure of smoking and on the choice of the comparison group. The 1985 paper by Thun et al. reported data on 70% of the workers. For these workers, the data indicated that as of 1982, 77.5% were current or former smokers compared to 72.9% current or former smokers among U.S. white males 20 years or older reported in the 1965 Health Interview Survey (HIS) conducted by the National Center for Health Statistics. It is clear that these 2 figures are not comparable since data from 1982 for the exposed group were compared with data from 1965 for the control group.

In the updated report by Thun et al. (1986), presented at the Fifth International Cadmium Conference in San Francisco, February 6, 1986, the authors provide a more meaningful comparison by limiting the

Table VII-9*

LUNG CANCER (ICD 162-163) MORTALITY BY CUMULATIVE EXPOSURE
WHITE MALE CADMIUM WORKERS HIRED ON OR AFTER 1/1/26
COMPARED TO U.S. DEATH RATES

EXPOSURE (cumulative mg/m^3) RANGE	MEDIAN	PERSON YEARS AT RISK	DEATHS	SMR	SRR
≤384	184.1	7005	2	53	.48
385-1920	795.6	5825	7(6)†	152(130)†	1.55(1.33)†
≥1921	2761.6	2214	7	280	3.45
		U.S. WHITE MALES		100	1.00

* Adapted from Thun et al. 1986, Table 7.
† Numbers in parentheses exclude one lung cancer death which was originally miscoded as being due to another cause.

Table VII-10*

LUNG CANCER (ICD 162-163) MORTALITY BY CUMULATIVE EXPOSURE
WHITE MALE CADMIUM WORKERS HIRED ON OR AFTER 1/1/26
COMPARED TO COLORADO DEATH RATES, 1950-79

Cumulative Exposure ($mg\text{-}days/m^3$)	PERSON YEARS AT RISK	DEATHS	SMR	SRR
≤384	7005	2	76	.70
385-1920	5825	7(6)†	212(182)†	2.29(1.96)†
≥1921	2214	7	387	5.09
	COLORADO WHITE MALES		100	1.00

* Adapted from Thun et al. 1986, Table 8.
† Numbers in parentheses exclude one lung cancer death which was originally miscoded as being due to another cause.

Table VII-11

SMOKING HABITS OF
CADMIUM-EXPOSED COHORT

	1982 Survey Cadmium-Exposed Cohort	1970 HIS Sample[1] Total	Operators & Kinded	Craftsmen & Foremen
Average age	61.5	44	39	42
% ever smoked	77.5[2]	76	79	83
% smoked a pack or more a day (includes current and former smokers)	10.8*[3]	44	49	53
Average length of smoking	--	23	20	22
% with > 20 cumulative pack years	53[2]	--	--	--

* This represented 25 or more cigarettes per day rather than 20 or more.

1 Health Interview Survey, conducted by National Center for Health Statistics, reported in Sterling and Weinkam 1976.

2 Varner 1983, based on 35% of workers.

3 Thun et al. 1986, based on 49% of workers.

smoking analysis to the 49% of the cohort for whom lifetime smoking histories were available. These data indicated that as of 1965 a larger percentage of the cadmium-exposed cohort were nonsmokers and a smaller percentage were heavy smokers compared to general population rates available from the HIS. The year 1965 was chosen since this was the midpoint of the study.

A different view of these data was presented by Varner (1984) who examined cumulative pack-years smoked by members of the cohort. He sugested that this cohort had far more heavy smokers than blue collar workers reported in the 1970 HIS, and that "smoking prevalence tends to be highest among blue collar workers." However, in the HIS survey the average age of the white males was 39 (operatives and kindred), 42 (craftsmen and foremen) and 44 (total sample). In the cadmium-exposed cohort the average age was no less than 53, and was estimated as 61.5. It is therefore surprising how similar some of the smoking characteristics of these populations are (see Table VII-11).

The percent who "ever smoked" was 77.5% in the cadmium-exposed cohort, and 76% in the total HIS sample. The data on the cadmium workers represented information from only 36% of the cohort. Given that the cohort under study was considerably older than the HIS sample, that the HIS survey was done about 10 years earlier than the survey of the cadmium cohort, and that different information was reported from these two surveys, the differences between the smoking habits of the total

HIS sample and those of the cadmium-exposed workers do not appear to be very large.

The magnitude of confounding from differential smoking habits can be assessed. A method to estimate the contribution of smoking to lung cancer mortality in the cohort is described by Axelson (1978). The method is applied to the lifetime smoking histories summarized by Thun et al. The calculations (summarized in Table VII-12) are based on information regarding smoking habits in the exposed group, smoking habits in the comparison group, and the relative risk for lung cancer at each level of smoking. In view of the data indicating a deficit of smokers in this cohort compared to the general population, the baseline SMR for lung cancer would have been reduced 30%.

It is unknown, however, whether the smoking histories of the 49% sample were representative of the cohort as a whole, and whether the histories themselves were biased, since they were collected retrospectively. While smoking may have confounded the relationship between cadmium and lung cancer, it is unlikely that smoking was responsible for all of the excess. Furthermore, if the smoking habits in this cohort were correctly reported, i.e., if the observed deficit of smokers was real, then the excess of lung cancer deaths is larger than originally

Table VII-12*

TECHNIQUE USED TO ADJUST FOR CIGARETTE SMOKING

	Percent of Population, 1965				
	Nonsmokers (1x)[3]	Moderate Smokers[1] (10x)	Heavy Smokers[2] (20x)	Rate Ratio of Overall Population Relative To Nonsmokers	Rate Ratio Relative To U.S.
POPULATION					
Exposed[4]	48.4%	40.8%	10.8%	6.724	0.70
U.S.	27.1%	53.0%	20%	9.571	1.00

* Thun et al., 1986

[1] 1-24 Cigarettes/day

[2] 25+ Cigarettes/day

[3] The numbers in parentheses refer to the relative risk for lung cancer associated with each level of smoking.

[4] Usable information available on 250 persons hired after 1926.

calculated. In other words, confounding due to smoking did not create the appearance of a nonexistent carcinogenic effect from cadmium; rather, the confounding reduced the apparent magnitude of cadmium's carcinogenicity.

(b) Arsenic

The plant employing the workers in this cohort refined cadmium metals and compounds from 1926 onwards. Between 1918 and 1925 it had functioned as an arsenic smelter. Therefore, the analysis by Thun et al. excluded workers employed prior to January 1, 1926. (For those employed prior to 1926 the lung cancer SMR was 714). Nevertheless it is possible that residues of arsenic contributed to the lung cancer excess for those first employed in 1926 or later.

To estimate the possible contribution of arsenic to lung cancer in this cohort, Thun et al.:

(1) identified the departments and job categories which were likely to have involved continued exposure to arsenic;

(2) calculated the proportion of person-years spent in areas with probable arsenic exposure based on personnel records (20%);

(3) evaluated industrial hygiene measurements to estimate air concentrations (range = 300 to 700 $\mu g/m^3$, Thun used midpoint = 500 $\mu g/m^3$);

(4) estimated the total years of employment for workers in the cohort (1728 years);

(5) based on (2),(3), and (4), estimated that total arsenic exposure amounted to 345.6 person-years of exposure to air levels of 500 $\mu g/m^3$;

(6) assumed a 75% respirator protection factor (i.e. inhaled exposures were 25% of air concentrations or 125 $\mu g/m^3$). This yielded a total exposure of 43,200 μg-years/m^3.

Using a risk assessment model developed by OSHA for arsenic carcinogenicity, Thun calculated that 43,200 $\mu g/m^3$ years of exposure to arsenic would contribute no more than .768 lung cancer deaths.

This may represent an overestimate of the contribution of the arsenic exposure to the lung cancer excess. The reasons submitted by Thun are as follows:

1) Only a fraction of jobs in the "arsenic areas" had exposures as high as the furnace area (500 $\mu g/m^3$)
2) The high exposure jobs were frequently staffed with brief employment-entry (sic) level workers who are not in the study cohort
3) Urinary arsenic levels on workers in the "high arsenic" areas from 1960-80 averaged only 46 $\mu g/l$ (equaling an inhaled arsenic of 14 $\mu g/m^3$)
4) Thus, assuming an average inhaled arsenic concentration of 125 $\mu g/m^3$ for these years overestimates the dose by 9 fold
5) ASARCO has previously argued that the OSHA risk assessment overestimates "by a factor of three or more" the expected increase in mortality from respiratory cancer.

(Thun, personal communication)

On the other side of this argument, the estimates of dose may not be reliable. The presumed relationship between urinary arsenic and inhaled arsenic may be incorrect, and is currently being reanalyzed (personal communication, Dr. Philip Enterline). Urinary measurements before 1960 were not available, and the earlier exposures would be expected to be greater. Furthermore, the figure of 125 $\mu g/m^3$ could be an underestimate since the respirator protection factor is based on a 1976 survey which compared air samples and personal samples. It is well known that earlier respirators were less effective, and in many cases compliance in earlier years was lower.

It is unclear, therefore, what the contribution of arsenic may have been to the overall excess of lung cancer deaths in the cadmium-exposed cohort studied by Thun et al. If the OSHA risk assessment model is correct, then under the assumption of no protection from respirators, the maximum number of excess lung cancer deaths attributable to arsenic would be 3.07 for the whole cohort. The excess attributable to arsenic is compared to the observed excess lung cancer deaths in Table VII-13 (unadjusted for smoking) and in Table VII-14 (adjusted for smoking). The adjustment for smoking is based on the analysis of smoking histories and assumes that smoking is independent of arsenic exposure within the plant, and that there is no interaction between these two exposures. The actual excess was 5.13 (unadjusted for smoking) or 8.39 (adjusted for smoking) if the whole cohort is considered; the excess was 9.00 (unadjusted for smoking) or 11.10 (adjusted for smoking) if only those with 2 or more years of exposure are included.

The last issue with respect to confounding concerns the combined effects of arsenic and smoking on lung cancer, which are more than additive, though probably less than multiplicative. Therefore, if any of the workers who were exposed to arsenic were smokers, there could also be confounding from the interactive effect of these two exposures. However, when relative risks are small (e.g., less than 1.3), there is very little difference between additive and multiplicative effects. Since it is unlikely that in this cohort the relative risk associated with either arsenic or smoking is larger than 1.3, the effect of any interaction is likely to be negligible. (If both relative risks are 1.3, multiplying yields 1.69, adding yields 1.6, difference = .09.)

In conclusion, given the low level of arsenic exposure and the evidence indicating a deficit of smokers in this cohort, DHS staff believes that the apparent association between cadmium exposure and lung cancer is not likely to be explained by confounding from smoking and/or arsenic exposure.

Finally, to summarize the DHS staff's findings with regard to the study by Thun et al.: the SMR of 2.3 in those with more than 2 years of cadmium exposure and the dose-response relationship are unlikely to be explained by chance, by bias, or by confounding from smoking and/or arsenic exposure. The staff of DHS concludes that the excess of lung

Table VII-13

THE POSSIBLE CONTRIBUTION OF ARSENIC TO THE EXCESS IN LUNG CANCER DEATHS

Observed	Expected[1]	Excess	Number Attributable To Arsenic
16	10.87	5.13	.768-3.07
16	7.00	9.00	---[2]

[1] Based on age- and calendar-year-specific lung cancer death rates for white males in the U.S. The first line refers to the whole cohort. The second line refers to workers with a minimum of two years employment (Thun et al. 1985).

[2] Not calculated but is certainly less than for the whole cohort.

Table VII-14

THE POSSIBLE CONTRIBUTION OF ARSENIC TO THE EXCESS IN LUNG CANCER DEATHS AFTER ADJUSTMENT FOR SMOKING[1]

Observed	Expected[2]	Excess	Number Attributable To Arsenic
16	7.61	8.39	.768-3.07
16	4.90	11.10	---[3]

[1] Assumes underlying SMR of .70 as shown in table VII-11, and no interaction.

[2] Based on age- and calendar-year-specific lung cancer death rates for white males in the U.S. The first line refers to the whole cohort. The second line refers to workers with a minimum of two years employment (Thun et al. 1985).

[3] Not calculated but is certainly less than for the whole cohort.

cancer deaths in the study by Thun et al. is best explained by exposure to high levels of cadmium. The DHS staff further concludes that while other confirmatory studies are desirable this study constitutes strong evidence of human carcinogenicity.

3. Mechanism

The biochemical mechanism(s) behind cadmium-induced mutagenic and carcinogenic effects is (are) not known. A number of possible mechanisms were discussed by Sunderman (1984). There is evidence that cadmium may act as an indirect mutagen or carcinogen but there are also substantial data indicating cadmium can directly interact with DNA and can therefore be a direct acting mutagen or carcinogen.

Cadmium can inhibit the activity of several individual enzyme activities and enzyme systems in vivo and in vitro. These include mitochondrial oxidative phosphorylation (Kamata et al. 1976), fidelity of DNA synthesis (Sirover and Loeb 1976), RNA synthesis (Stoll et al. 1974), protein synthesis (Norton and Kench 1977), and hepatic mixed function oxidase enzyme activities (Teare et al. 1977; Furst and Mogannam 1975). The effect on some enzyme activities may be the result of displacement by cadmium of the metal ion, such as zinc, in a metalloenzymes. If cadmium inhibits or alters enzyme activities involved in DNA replication or repair, somatic mutations may result. Cadmium

may also act as a cocarcinogen by altering the metabolism of a procarcinogen (Jennette 1981).

Cadmium has also been found to directly bind to isolated DNA at specific high affinity sites (Waalkes and Poirier 1984) and to cause mispairing in complexes formed between synthetic polynucleotides (Murray and Flessel 1976). Other metals, such as zinc, magnesium, and calcium, can antagonize the binding of cadmium to isolated DNA, but cadmium was found to have the highest affinity for the binding sites (Waalkes and Poirer 1984). In an in vivo study (Hidalgo and Bryan 1977), labeled cadmium was found to localize in the nucleus of liver cells. It was found to be concentrated more in nonhistone than histone proteins.

The direct interaction of cadmium with DNA and the number of positive mutagenic and clastogenic studies suggest that cadmium may have a direct effect on DNA. The interaction between cadmium and other metals found by Waalkes and Poirer (1984) may explain the inhibitory effect of these metals on cadmium-induced carcinogenicity.

4. Conclusion

The staff of the Department of Health Services (DHS) agrees with the International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA) that there is sufficient evidence to conclude that cadmium is an animal carcinogen. The DHS staff's

conclusion is based in part on the findings of distant site tumors, interstitial cell tumors of the testis, following subcutaneous administration of cadmium salts to two species, rats and mice (Gunn et al. 1983, 1964; Levy et al. 1973). EPA (1985) presents a good review of literature supporting the use of distant site tumors as evidence for the carcinogenic potential of a compound following subcutaneous injection. Although injection site tumors have also occurred, these are not considered sufficient evidence of a compound's carcinogenic potential. IARC (1982) also used the evidence of distant site tumors as the basis for their conclusion. Additional supporting evidence, not available at the time of the IARC decision, includes the studies of Poirier et al. (1983) and Takenaka et al. (1983). Poirier et al. (1983) found a significant increase in distant site tumors of the pancreas and the testis in rats given subcutaneous injections of cadmium chloride. Takenaka et al. (1983) observed a significant increase in lung tumors in rats exposed to a cadmium chloride aerosol. Both of these findings were also used as a basis for the DHS staff's conclusion.

The IARC last evaluated cadmium for carcinogenicity before the results of the study by Thun et al. were available. The EPA most recently evaluated cadmium in 1985 and concluded "there is limited epidemiologic evidence that inhaled cadmium is dose-related to lung cancer in exposed workers" (EPA 1985). The DHS staff considers all animal carcinogens to be potential human carcinogens. The DHS staff finds that the epidemiologic evidence supports an inference of a causal association between cadmium and respiratory cancer for the following reasons: (1)

the negative studies (Inskip et al. 1982, Anderson et al. 1984) had low statistical power and/or poor exposure data, (2) positive findings were present in several studies utilizing different cohorts and different types of analyses (Thun et al. 1985, Sorahan and Waterhouse 1983, Armstrong and Kazantzis 1983), (3) some of these studies found that other smoking-related causes of death were not elevated (Sorahan and Waterhouse 1983, Thun et al. 1985), (4) the single study with detailed quantitative exposure data showed a highly significant dose-response (Thun et al. 1985), (5) there were no sources of bias which could explain this finding, and (6) the same study, in examining confounding, found a potential deficit of smokers among the exposed workers, and estimated only a small contribution from arsenic, indicating that the positive finding was unlikely to be explained by these confounders.

The DHS staff concludes that while more confirmatory studies would be desirable before judging the sufficiency of the evidence, there is a high probability that cadmium is carcinogenic in humans.

VIII. Threshold Discussion

The noncarcinogenic effects of cadmium are believed to occur through mechanisms that have threshold exposure levels at and below which no effect will occur. The carcinogenic activity of cadmium may occur through a mechanism for which no threshold exposure level exists. Such a mechanism would probably involve direct interaction of cadmium with nuclear DNA. Biochemical studies have shown that there are high affinity binding sites for cadmium on isolated DNA and that cadmium can cause mispairing of synthetic polynucleotides (Walker and Poirier 1984; Murray and Flessel 1976). As described further in Section VII.J.1, there is suggestive but inconclusive evidence that cadmium is genotoxic.

There are mechanisms proposed by which compounds may induce a carcinogenic response without a direct effect on nuclear DNA. These mechanisms may have threshold exposure levels associated with them. Cadmium may also act by reducing the fidelity of DNA synthesis (Sirover and Loeb 1976). Cadmium may act as a cocarcinogen by altering the metabolism of a procarcinogen (Jennette 1981). Tissue injury, such as that observed in the testes, may also act as an indirect mechanism. However, these mechanisms are speculative: there is no compelling evidence that they are actually responsible for the observed carcinogenic response of cadmium.

In light of the above considerations, particularly the absence of compelling evidence of a threshold mediated mechanism, DHS staff concludes that cadmium's carcinogenicity should be treated as a nonthreshold phenomenon.

IX. Risk Assessment

Both carcinogenic and noncarcinogenic effects have been identified in the spectrum of cadmium-induced toxicity. Since there is a qualitative difference in how these processes occur, the hazards posed by these effects must be quantified in different ways. However, once the quantitative risks are determined, a judgement about the greatest potential hazard posed by a compound can usually be made. Below, the noncarcinogenic hazard posed by cadmium will first be quantified followed by a quantification of the carcinogenic hazard.

A. Noncarcinogenic Risk

Cadmium has been found to induce a number of noncarcinogenic toxic effects in experimental animals and humans. These effects include hypertension, endocrine changes, hepatotoxicity, osteomalacia and osteoporosis, anemia, immunosuppression, emphysema and pulmonary function changes, renal toxicity, fetotoxicity, and teratogenicity. Several of the effects have occurred in experimental animals at low exposure levels. Hypertension occurred in rats given drinking water containing as little as 0.1 ppm of cadmium over an 18-month period (Perry et al. 1977). This is an approximate intake of 5 μg/kg-day. Sporn et al. (1970) reported finding changes in liver enzyme activity in rats given drinking water containing 1 ppm (a dose of approximately 50 μg/kg-day). Effects suggesting immunosuppression occurred in mice receiving drinking water containing 3 ppm (a daily dose of approximately 500 μg/kg-day)(Koller et al. 1975, Exon et al. 1974).

Respiratory effects have been observed in experimental animals and humans at airborne concentrations of around 20 $\mu g/m^3$ but not at levels below 15 $\mu g/m^3$; these are equivalent to daily doses of approximately 6.0 and 4.5 $\mu g/kg$-day, respectively. Although these various effects have been reported to occur at relatively low levels of exposure, several authors and organizations have considered renal toxicity to be the most sensitive noncarcinogenic effect (Friberg et al. 1974, WHO 1977, and EPA 1981). Because the strongest and most abundant epidemiological evidence exists for this site, the staff of DHS has used renal toxicity as the basis for quantitative noncarcinogenic hazard assessments performed on cadmium.

As discussed in Section VII.H, Friberg et al. (1974) estimated that a retention rate of between 6.6 and 24.6 μg/day of cadmium would be necessary for the renal cortex concentration to reach 200 $\mu g/g$ wet weight over a 50-year period (see Table VII-1). Kjellström et al. (1984) estimated that about 10 percent of a human population would show signs of renal toxicity at that concentration in the renal cortex. To achieve such a rate of cadmium retention from inhalation alone, Friberg et al. (1974) estimated that the ambient airborne concentration needed to be from 0.65 to 2.5 $\mu g/m^3$, assuming a 50 percent absorption of inhaled cadmium. The most likely concentration was estimated to be 1.5 $\mu g/m^3$, based on the assumption of a 19-year biological half-life for cadmium (see Section V.D).

The renal cortex concentration of 200 $\mu g/g$ wet weight tissue is not a threshold concentration but, at best, one that would produce an effect

in only 10 percent of a population. No threshold level has actually been determined, although renal toxicity is believed to have a threshold renal cortex concentration at which no toxicity will occur. An ambient air concentration of 1 ng/m^3 (0.001 μg/m^3) of cadmium is 650 to 2500 times less than the ambient air concentrations (0.65 to 2.5 μg/m^3), estimated by Friberg et al. (1974), that will lead to a renal cortex concentration of 200 μg/g wet weight following lifetime exposure. Although no threshold concentration for renal toxicity has been determined, staff members of DHS believe that the magnitude of the difference between exposure to lifetime ambient air cadmium concentrations at 1 ng/m^3 and at those concentrations that will induce renal toxicity in 10 percent of the population is sufficiently large so that there is little, if any, risk of renal toxicity from exposure to 1 ng/m^3 of cadmium. Exposure to an ambient air concentration of 10 ng/m^3 may pose a risk if the most conservative assumptions by Friberg et al. (1974) are correct. If the most likely assumption by Friberg et al. is correct, then exposure to an ambient air concentration of 10 ng/m^3 probably does not pose a risk of renal toxicity.

B. Carcinogenic Risk

Both experimental animal studies and epidemiological studies of worker population have indicated cadmium is carcinogenic. Quantitative assessments have been performed on both of these types of studies in order to obtain a range of risks. The quantitative risk assessment using the animal studies is discussed first, followed by a presentation

of the quantitative risk assessment based on the human epidemiological study.

1. Quantitative Cancer Risk Assessment Based on Animal Data

The animal study chosen as the basis for a quantitative risk assessment was that reported by Takenaka et al. (1983, see Appendix A). This is the only adequate long-term inhalation study and, as such, is the most relevant study to assess the carcinogenic potential of cadmium as an air pollutant. Several ingestion studies have been performed, but none showed a positive response. Injection studies have been positive for injection site tumors and tumors at remote sites. However, parenteral exposure is not normally considered an appropriate route for quantitative risk assessment.

Lung tumors were the only neoplasms found to be significantly increased in the study reported by Takenaka et al. (1983). The tumor incidences and exposure levels used for the low-dose extrapolation are given in Table IX-1. Assumptions used to determine these values are described below.

The tumor incidence data used in this analysis combines the three types of malignant lung tumors identified in the animal study. The separate incidence rates for each tumor type are given in Table VII-4. These tumor types were combined because they were all found in the sametissue and were all carcinomas. Two animals had one tumor identified

Table IX-1

Exposure Levels and Tumor Incidences
Used in Low Dose Extrapolation

Exposure Level[a] in $\mu g/m^3$	Incidence[b] (No. of animals with Tumors/ No. of animals examined)
0 (0)[c]	0/38
2.2(13.4)	6/39
4.1(25.7)	20/38
8.3(50.8)	25/35

[a] Human equivalent exposure values as cadmium, see text for explanation of how these values were determined.

[b] These included all malignant lung tumors. Lung tumor types identified were adenocarcinoma, epidermoid carcinoma, and mucoepidermoid carcinoma.

[c] Numbers in parentheses are average measured airborne cadmium concentrations during rat study.

Source: Takenaka et al. 1983.

as an adenocarcinoma and a second one identified as an epidermoidcarcinoma. These animals were only counted once in the incidence data.

The exposure levels used in the low-dose extrapolation calculations were human equivalent lifetime levels based on the animal exposure levels. Two assumptions were used to make these conversions. The first assumption was that the partial lifetime exposure of 18 months that the rats received could be made equivalent to a full lifetime exposure of 24 months by multiplying the average measured exposure

level by the ratio of the length of exposure to length of expected lifetime:

18 months/24 months = 0.75.

Since the animals were exposed for 23.5 hours per day, no conversion factor was used to make exposure equivalent to a 24 hours per day exposure expected for the human population in this assessment.

The second assumption was that the human equivalent ambient exposure concentrations could be calculated based on a body surface area scaling factor from the experimental exposure levels. However, a number of different scaling factors could have been used. Scaling factors take into account differences in body weight, surface area, metabolic rate, and/or lifetime. The staff of DHS has previously found that none of the commonly used scaling factors is empirically most appropriate for animal-to-human dose conversion in low-dose cancer risk extrapolation. Since several scaling factors appeared to give acceptable results, DHS staff members have decided to use surface area because it gives an intermediate measure of dose compared to other scaling factors and because surface area is related to metabolic rate, which may affect an organism's response to a carcinogen.

To use the surface area scaling factor, experimental exposure levels, in $\mu g/m^3$, are first converted to a daily dose, in $\mu g/kg\text{-}day$. Assumptions used for this conversion were that the rats inhaled 0.144

m^3/day and that 100 percent of the inhaled cadmium chloride aerosol is deposited in their lungs. (An absorption factor was not used because the tumors occurred at the site of contact and the importance of systemic absorption is not known for this effect.) Average group body weights provided by the authors, at 18 months into the study, were used for these conversions. These body weights were 0.425, 0.438, and 0.424 kg for exposure group levels 13.4, 25.7, and 50.8 $\mu g/m^3$, respectively. The calculation was performed as follows:

$$Ea(Va/Wa) = Da$$

where Ea is the experimental exposure level, which has already been transformed to a full lifetime exposure level; Va is the daily volume of air inhaled by a rat; Wa is the average group body weight; and Da is the daily dose level.

Conversion of the animal daily dose level Da to a human daily dose level based on surface area was done by a method used by EPA (1980b). This was accomplished by the following formula:

$$Dh = Da(Wa/Wh)^{1/3}$$

where Dh is the human equivalent daily dose and Wh is the assumed average human body weight, 60 kg.

Finally the human equivalent daily dose was converted to a human equivalent ambient air concentration by assuming an average daily human inhalation volume of 18.05 m^3/day.

$$Dh(Wh/Vh) = Eh$$

where Vh is the assumed human daily inhalation volume and Eh is the human equivalent exposure level.

A sample calculation for the experimental animal group exposed to 13.4 μg cadmium/m^3 is given below:

$$13.4\ \mu g/m^3 \times 0.75 = 10.05\ \mu g/m^3 = Ea$$

$$10.05\ \mu g/m^3 \times \frac{0.144\ m^3/day}{0.425\ kg} = 3.4\ \mu g/kg\text{-}day = Da$$

$$3.4\ \mu g/kg\text{-}day(0.425\ kg/60\ kg)^{1/3} = 0.65\ \mu g/kg\text{-}day = Dh$$

$$0.65\ \mu g/kg\text{-}day \times \frac{60\ kg}{18.05\ m^3/day} = 2.2\ \mu g/m^3 = Eh$$

Results of Low-Dose Extrapolation

Using the multi-stage extrapolation model (See Appendix B), the estimated excess human cancer risk from exposure to cadmium was

calculated based on lung tumor incidence in rats exposed to cadmium chloride aerosol, as reported by Takenaka et al. (1983).

The computer program, GLOBAL79, for low-dose extrapolation based on the multistage model, calculates the extra risk function by maximizing the likelihood function of the input data. The maximum likelihood estimate (MLE) and the 95% upper confidence limit (UCL) of excess risk can then be determined for any exposure level. The 95% UCL for extra risk is always linear at low doses, which is conceptually consistent with the linear nonthreshold theory of carcinogenesis. The slope of the 95% UCL, q*, is taken as a plausible upper bound of carcinogenic potency.

Because the animal exposure levels for cadmium were converted to human equivalent exposure, the 95% UCL, q*, is a measure of excess cancer risk for humans. If the lifetime daily exposure is expressed in ($\mu g/m^3$), then q* can be considered as the excess risk associated with this exposure. Since q* for humans is a measure of excess lifetime cancer risk associated with exposure to one unit (in $\mu g/m^3$) cadmium, it is termed the <u>unit risk</u>. The 95% UCL of excess risk may be approximated for any low level exposure to cadmium by the equation:

$$R = \text{unit risk} \times \text{dose},$$

where R is the 95% UCL of excess lifetime cancer risk. The unit risk for cadmium, based on the lung tumor incidence data, is 1.81×10^{-1} $(\mu g/m^3)^{-1}$.

Although the staff of DHS believes that the multistage model is the appropriate method to estimate low dose risk, other models have been used to show the range of risk estimates that can be obtained (See Appendix B). For comparison, the maximum likelihood estimate and 95% UCL of excess human lifetime cancer risk based on liver tumor incidence in male rats are presented in Table IX-2 for each model at two possible environmental exposure levels. The environmental ambient levels expected in California are believed to range around 0.001 to 0.003 $\mu g/m^3$ (1 to 3 ng/m^3, see Part A). The 95% UCL dose-response curve for each model can be seen in Figure IX-1. Usually, the multi-stage model is the most conservative model (finding the highest risk) at low dose levels. The probit is generally the least conservative model, followed in order by the gamma multi-hit, logit, and Weibull models. In this case, the multistage model is the most conservative, as expected, followed by the Weibull, gamma multi-hit, logit, and probit models.

Table IX-2

Maximum Likelihood Estimates and 95% Upper Confidence Limits for Excess Lifetime Cancer Risk from Exposures at 10^{-3} and 10^{-2} $\mu g/m^3$ Based on Different Low Dose Extrapolation Models[a]

	Ambient Air Concentration ($\mu g/m^3$)			
	10^{-2}		10^{-3}	
Model	MLE[b]	UCL[c]	MLE	UCL
Multistage	$1113/10^6$	$1807/10^6$	$111/10^6$	$181/10^6$
Probit	$< 1/10^6$	$< 1/10^6$	$< 1/10^6$	$< 1/10^6$
Logit	$13/10^6$	$68/10^6$	$< 1/10^6$	$1/10^6$
Weibull	$285/10^6$	$1140/10^6$	$16/10^6$	$79/10^6$
Gamma Multi-Hit	$42/10^6$	$145/10^6$	$1/10^6$	$4/10^6$

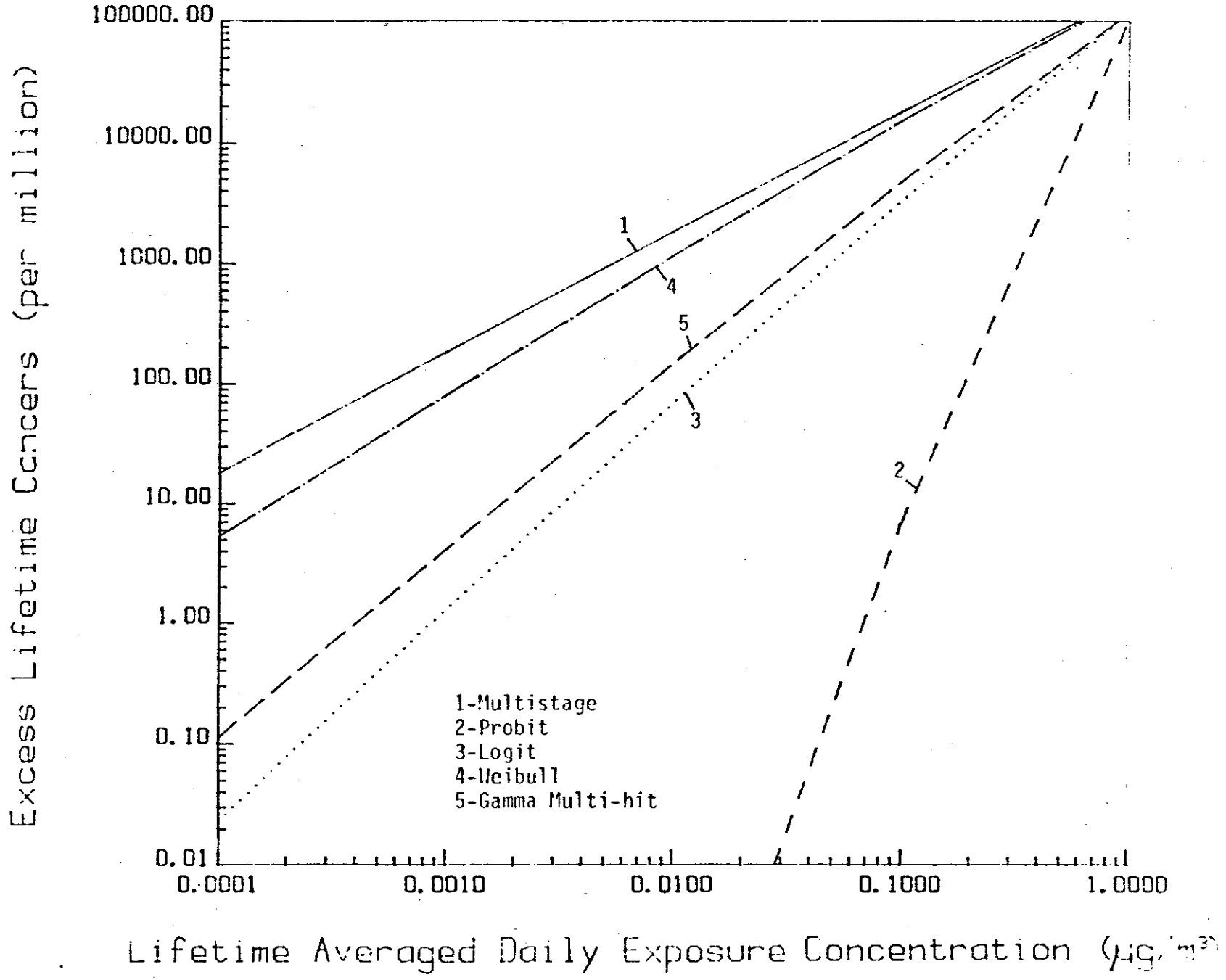
[a] Based on lung tumor incidence in male rats exposed to cadmium chloride aerosol, as reported by Takenaka et al. (1983)

[b] Maximum Likelihood Estimate, expressed as excess lifetime cancer cases per million population.

[c] 95% upper confidence limits, expressed as excess lifetime cancer cases per million population.

Figure IX-1

ESTIMATED HUMAN EXCESS LIFETIME CANCER RISK BASED ON MALE RAT LUNG TUMORS USING THE 95% UCL



2. Quantitative Cancer Risk Assessment Based on Human Data

Department of Health Services (DHS) staff conducted a quantitative cancer risk assessment for cadmium using the data from the occupational mortality study by Thun et al. (1985) and extrapolating to ambient levels in California. The strengths of this study are described elsewhere in this document (Section VII.J.2). The exposure data in this study were based on industrial hygiene measurements and individual work histories. These measurements consisted of historical area monitoring samples and, when appropriate, were adjusted to reflect respirator protection in departments where respirators had been worn. For workers employed 6 months or longer in production areas of the plant the person-years of follow-up were divided into 3 categories according to cumulative exposure in mg-days/m^3, (see Table IX-3). The risk of death from lung cancer for each exposure group was measured by the standardized mortality ratio (SMR). The data indicated a clear dose-response, with SMRs of 53, 152 and 280 for the low, moderate and high exposure groups. Because the study related quantified exposure levels to quantified measures of lung cancer risk, the data were suitable for a risk assessment.

DHS staff emphasizes that the risk estimates derived in conducting any risk assessment are not exact predictions, but rather represent best estimates based on current scientific knowledge and methods. It is important to recognize that uncertainties arise both in the data and in the extrapolation process, and that these uncertainties necessitate the use of assumptions. In its presentation of this risk assessment, the DHS staff has explained the assumptions made at each step, and the direction in which each assumption affected the risk estimates.

The choice of assumptions involves scientific judgment. Guided by our mandate to protect the public health, the DHS staff has chosen to use linear models for extrapolation purposes, because these models are likely to be health-conservative. With regard to assumptions about the data, the DHS staff has utilized the median exposure levels and maximum likelihood risk estimates. This approach leads to a plausible upper bound for risk estimates.

The carcinogenic risk assessment for cadmium is discussed in three sections which cover the following:

(1) the limitations of the data collected and reported by Thun et al.;

(2) the model which was fitted to the data, its mathematical representation, and the assumptions; and

(3) the application of the model to the general population to obtain a unit risk and upper confidence limit for this unit risk.

a. Limitations of the data used for quantitative risk assessment

Uncertainties stemming from the data on which the risk assessment was based fall into four main categories: (1) the accuracy of the exposure assessment for workers in the cohort, (2) the accuracy of the response or cancer mortality measurements, (3) the potential effects of confounding factors and (4) the application of the observed dose-response relationship to the California general population. A full discussion of potential confounding in this study is found in Section VII.J.2, Respiratory cancer - Thun study. The first three issues relate to internal validity in the measurement of a dose-response relationship among a group of cadmium-exposed workers; the fourth is an issue of external validity or generalizability beyond the study population.

(i) Uncertainties in the exposure estimates

Industrial hygiene area samples provided the basis for assessing exposure of individuals. For each job category, a quantitative exposure level was assigned. Each day of each worker's employment was classified into one of seven exposure-based job categories. While samples had been collected and measured beginning in the 1940's, the period of potential exposure for this cohort was 1926 - 1969 (inclusive). Two adjustments were made to these measurements: (1) conversion from area samples to personal exposure estimates was based on a 1973 - 1976 survey which compared area and personal samples; (2) adjustment of the personal exposure estimates to reflect respirator effectiveness was based on a 1976 survey of respirators.

Uncertainty as to the validity of the exposure estimates stems from (i) the application of 1940's measurements to earlier periods, (ii) the application of department-based data to individual workers, (iii) the use of a ratio determined in the 1970's for converting area samples to personal exposures for the entire exposure period, and (iv) the use of a respirator effectiveness factor determined in 1976 for the entire exposure period. The assumptions of (i) and (iv) are likely to result in underestimation of exposure, while the assumptions of (ii) or (iii) could be biased in either direction. The DHS staff knows of no way to quantify these uncertainties.

(ii) Uncertainties in the risk estimates

Loss to follow-up was low (2%); nevertheless, if any of the 12 whose vital status was not ascertained did die of lung cancer, the calculated

SMRs would be lower than they should be, and therefore the risk estimates derived by DHS would also be too low.

One of the lung cancer deaths in the middle exposure category was originally miscoded as a non-lung cancer death. For consistency with the comparison population (general population rates inevitably include some miscodings of the cause of death), this death should not be counted as being due to lung cancer. In this risk assessment, the estimates were calculated by excluding this death. A comparison showed that inclusion of this death as due to lung cancer did not substantially alter the risk estimates.

The original analysis of Thun et al. (1985) used U.S. lung cancer death rates for comparison with this cohort (Table VII-9) because state rates were not available before 1950. An updated report (Thun et al. 1986) includes estimates of SMRs based on Colorado rates in which the 1950 rates were assumed to hold for the earlier years (Tables VII-10). The DHS estimated excess risk using both the U.S. and Colorado lung cancer death rates. As shown below, these estimates are virtually identical.

Uncertainty with regard to the measures of risk reported by Thun et al. are rather minor. With the exception of the unknown outcomes for those lost to follow-up, DHS staff has incorporated these uncertainties (stemming from the miscoding and the choice of control population) into its analysis.

(iii) Nature of the cohort and occupational exposure

The exposures of the workers in the study tended to be acute and occurred within a short time span, while those of the general population occur at low levels over a lifetime. It may be that a high, short-term exposure which overwhelms the body's defense mechanisms is necessary for cadmium to exert its carcinogenic effect. There is no clear evidence, however, that cadmium operates in this way. In an animal study, at an exposure level of 1.6 mg/m^3, initial pulmonary damage appeared to be repaired even under continued exposure (Hart, 1986). Therefore, DHS has made the health-conservative assumption that cumulative exposure is the appropriate measure for evaluating the dose-response relationship between cadmium and lung cancer mortality.

Since white male workers in Colorado constitute the members of the cohort, in order to estimate risks to the general California population it has been assumed that dose-response relationships observed in Colorado white male workers are applicable to California residents of all ages, including: nonwhites, females, and nonworkers. DHS staff has used a model which quantifies the overall health difference between the workers in the study and those in the general population of the same race, sex and age. That is, an estimate was made not only of cadmium's carcinogenic potency, but also of the "healthy worker effect". In effect, this risk assessment assumes that the dose-response relationship established for white males in the general population of the same ages as the workers is applicable to white males of other age groups and to females and nonwhites of all ages. The DHS staff knows of no way to quantify the uncertainty stemming from this assumption.

(iv) Confounding

Uncertainty stemming from potential confounding by smoking or arsenic has been discussed in detail elsewhere in this document (See Section VII.J.2 Human Studies, Respiratory Cancer : Thun study).

b. Modeling of the Data for Cancer Risk Assessment

(i) Exposure assumptions for the modeling

As discussed above, the first assumption of the risk assessment is that the lifetime cumulative exposure to cadmium can be used as a summary measurement for determining carcinogenic potency. In other words, it is assumed that total lifetime dose determines cancer risk, regardless of whether it is inhaled in a workplace setting at the mg/m^3 level, or whether it is inhaled over a whole lifetime from ambient air at the ng/m^3 level. The DHS staff recognizes that this is a simplistic assumption and that dose-rate may influence the magnitude of carcinogenic effects. In the case of cadmium, the data are insufficient to quantify the dose-rate effect on carcinogenesis. The assumption to ignore dose-rate is a health-protective assumption since the environmental exposures involve lower dose-rates than were prevalent among the workers. The median cumulative exposure in each of the three exposure groups designated by Thun et al. was used in the risk assessment (see Table IX-3). (These medians, though not in the published report, were provided by Dr. Thun, personal communication.)

Table IX-3

EXPOSURE LEVELS OF
WORKERS IN STUDY BY
THUN ET AL.

	Cumulative Exposure in mg-days/m^3			Equivalent Lifetime Dose Rate* in $\mu g/m^3$
	Range Reported by Thun et al.	Median	Median Adjusted for 240 Workdays/year	Median
Low	≤584	280	184.1	2.7
Middle	585-2920	1210	795.6	11.8
High	≥2921	4200	2761.6	41.0

* Assumes 24 hours/day exposure and an estimated average lifetime of 61.5 years.

A second assumption regarding exposure is that particle size distribution in the occupational setting of the Thun et al. study is similar to that of ambient California air. There is insufficient information to determine the validity of this assumption, or to determine whether this assumption leads to an underestimate or overestimate of actual risk.

(ii) Justification of model

A linear model which incorporates a parameter for the "healthy worker effect" was fitted to the data and evaluated for goodness-of-fit. DHS staff considers linear models most appropriate for extrapolating human cancer risks at low doses from human data at high doses. This position is based on the view that risk estimates should represent plausible upper bounds. The concept of a "plausible upper bound" is distinct from a "worst-case scenario," as explained below.

Current scientific opinion supports the view that the assumption of linearity is likely to be health-conservative, and should therefore lead to an upper bound estimate of low-dose risks. The actual risks may be lower than those estimated, but are unlikely to be higher, though this possibility cannot be completely ruled out. Therefore the "upper bound" aspect of the DHS staff risk estimate is mainly a reflection of the linearity assumption.

On the other hand, the use of observed mortality data and reasonable exposure estimates renders these estimated risks plausible. If the estimates of exposure had been based on assumptions that were extreme (e.g., only using the lowest measurements, thereby inflating the potency estimate) or if instead of the observed deaths, an upper confidence limit had been used, then the resulting risk estimates would have been derived from a "worst case scenario." Therefore the "plausible" aspect of the DHS risk estimate stems from the use of available and reasonable estimates of exposure and observed mortality data.

Finally, the use of the slope estimated by an iterative least squares (Gauss-Newton) method yields a best estimate for a plausible upper bound of risk. The 95% (two-tailed) upper confidence limit on the slope of the linear model yields an upper confidence limit for the risk estimate. It represents, under the assumption of linearity, an estimate of slope that is likely to be too low only 2.5% of the time.

(iii) Specification of model

A Poisson regression model was fitted to the data. In this model the observed deaths are a function of two variables: the dose and the expected deaths. The function has two parameters: one for the carcinogenic potency of cadmium, the other to account for the healthy worker effect.

Let Obs_i = observed deaths in exposure group i

Exp_i = expected deaths in exposure group i based on the indirect method of age adjustment

d_i = median dose received by group i

Then the model is expressed as:

$$E[\ Obs_i] = (1+\beta d_i) \cdot \alpha \cdot Exp_i$$

where $E[\cdot]$ represents the expectation of a random variable,

α = healthy worker effect, and

β = potency of cadmium per unit dose.

This model predicts that in the absence of cadmium exposure (d_i=0), the observed deaths will equal the expected deaths times some factor which distinguishes the workers from the general population, a factor which can be termed the "healthy worker effect." The appropriateness of this model is indicated by the mortality experience of the low exposure group, which had an SMR for lung cancer of 53. (The cohort also had a low SMR for cardiovascular deaths.) This model therefore separates the carcinogenic effect of cadmium from the opposing, healthy worker effect. Using the nonlinear regression procedure (NLIN) of the statistical package produced by the SAS Institute, the parameters were estimated at:

$\hat{\alpha}$ = .500 (unitless parameter) and

$\hat{\beta}$ = .0017 (cumulative mg-days/m^3)$^{-1}$.

The 95% (two tailed) upper confidence limit for β was .0079, and the χ^2 goodness-of-fit statistic was .15 (1 df, p=.70). Lung cancer deaths predicted by the model are compared with the observed lung cancer deaths for the three exposure groups in Table IX-4.

Table IX-4

LUNG CANCER DEATHS
AMONG CADMIUM-EXPOSED WORKERS:
OBSERVED AND PREDICTED

		CUMULATIVE EXPOSURE GROUPS		
		Low	Middle	High
OBSERVED *		2	6	7
PREDICTED:	LINEAR RELATIVE RISK MODEL WITH			
	HEALTHY WORKER EFFECT			
	U.S. Controls	2.49	5.48	7.23
	Colorado Controls	2.48	5.50	7.22
	NO HEALTHY WORKER EFFECT			
	U.S. Controls	4.16	6.69	6.42[a]
OBSERVED[b]*		2	7	7
PREDICTED:	LINEAR RELATIVE RISK MODEL WITH			
	HEALTHY WORKER EFFECT			
	U.S. Controls	2.94	5.99	7.44

* Data of Thun et al. 1985

a The prediction of fewer deaths in the high exposure group than in the middle exposure group reflects a larger number of person-years in the middle exposure group.

b The lower part of this table represents the Thun et al. data in which an originally miscoded death has been corrected to be due to lung cancer.

As discussed above (Section IX.B.2.a.ii Uncertainties in the risk estimates), the uncertainties in the data (due to miscoding of one lung cancer death and the use of U.S. rather than Colorado population rates) were evaluated by fitting two alternate versions of these data. In addition, the model was altered by removing the healthy worker parameter, for the purpose of comparison. (See Table IX-4.):

(1) Using expected deaths based on Colorado rates rather than U.S. rates, the predicted deaths were almost identical, though the estimate of α was different ($\hat{\alpha} = .727$, not shown in table). The model therefore behaves as it should, i.e.: (1) the estimate of the dose effect should not depend on the comparison population; (2) the difference between these workers and the population of Colorado should be less than the difference between the workers and the U.S. population (that is, $\hat{\alpha}$ was closer to 1 using the Colorado population).

(2) Inclusion of the miscoded lung cancer death from the middle dose group (i.e. fitting the model to observed deaths of 2,7 and 7 rather than 2,6 and 7 for the three dose groups) yielded very similar results.

(3) For comparison, the linear model without a healthy worker parameter was fitted to the data. As seen in Table IX-4, the fit was not as good, particularly for the low dose category.

c. Application of the model to the California population

With these estimates of the parameters, the model was then applied to the California population to predict the excess number of lung cancer deaths

induced by cadmium exposure. The mathematical details are shown in appendix D.

First, a current life table was produced for California males and females separately, using five-year age intervals (see Table D-1a and D-1b). The life table allows one to adjust for competing causes of mortality in evaluating the risks due to a particular cause. The background hazard of lung cancer death for each five-year age interval was calculated using 1980 census data for California (Bureau of the Census, 1982) and age-specific death rates for California from 1979-80 vital statistics data (California Department of Health Services, 1982) by standard statistical techniques (Chiang 1984). These were then summed over a lifetime: the last entry of the last column in Table D-1a and D-1b represents, for males and females respectively, the cumulative probability of dying of lung cancer to the end of that age interval, i.e. age 79.

Next, using the estimated value for β and setting $\alpha = 1$ for the general population (i.e. no healthy worker effect), the hazard of lung cancer death given a continuous lifetime exposure to 1 ng/m^3 cadmium was calculated from the model. Using these hazard rates, a new life table was constructed (Tables D-2a for males and D-2b for females). Subtracting the background probability of a lung cancer death from that obtained for an exposed population results in a unit risk of 1.6 excess lung cancer deaths per million persons in California due to a continuous lifetime exposure of 1 ng/m^3 cadmium in air. Table IX-5 summarizes these risk estimates.

TABLE IX-5

LIFETIME PROBABILITY OF
LUNG CANCER DEATH

	MALES	FEMALES	
BACKGROUND	.0554577	.0248524	
EXPOSED[a] no lag			
LSE[b]	.0554599	.0248534	
UCL[c]	.0554731	.0248593	
EXPOSED[a] 10 year lag			
LSE	.0554595	.0248532	
EXCESS DUE TO EXPOSURE			TOTAL[d]
LSE	2.2×10^{-6}	1.0×10^{-6}	1.6×10^{-6}
UCL	15.4×10^{-6}	6.9×10^{-6}	11.6×10^{-6}

[a]Exposed continuously to 1 ng/m^3 Cd in ambient air.
[b]LSE - least squares estimate.
[c]UCL - 95% upper confidence limit.
[d]Assumes 50% of population for each sex.

Using the upper confidence limit for β instead of the least squares estimate yields an upper limit of 11.6×10^{-6} for the unit risk of excess lung cancer deaths per 1 ng/m^3 cadmium in air (based on Tables D-3a and D-3b). An alternative analysis which assumes that the effect of an exposure on subsequent lung cancer deaths requires a 10-year latency period did not alter the estimates of excess risk (see Tables D-4a and D-4b).

The estimated unit risk for excess lung cancer deaths due to 1 ng/m^3 lifetime exposure of cadmium is 2×10^{-6}. The upper 95% confidence limit of this estimate is 12×10^{-6}.

The DHS staff recommends that the upper 95% confidence limit estimate be used for regulatory purposes, rather than the best estimate, for two reasons: (1) the epidemiologic evidence is suggestive of cadmium carcinogenicity for several urogenital sites, and (2) the application of a dose-response relationship observed in adult working males to the general population assumes equal potency across all ages and both sexes.

This risk assessment uses only one site, respiratory tract cancers. As stated in Section VII.J.2, there is evidence suggesting an association between cadmium exposure and renal, bladder, and prostate cancer. Since quantitative exposure data were not available for those studies that showed increased risk for these cancers, it was not possible to conduct an analysis similar to that conducted for respiratory cancer. Deaths from these three cancers are much

rarer than respiratory cancer deaths, and the excess number of deaths from all three combined is likely to be far less than the number of excess respiratory cancer deaths for a given level of cadmium exposure. Nevertheless, some margin above the least squares estimate of unit risk would be desirable, in order to include the added risk for deaths from cancer at other sites.

The assumption of equal potency for cadmium carcinogenicity across all ages and both sexes could result in underestimates of risk for several reasons. Rapidly proliferating tissues may be more susceptible to carcinogenic agents than cells which are proliferating at a slower rate since the opportunities for errors in DNA replication are greater at these times. Lung growth occurs through childhood and puberty. Secondly, where air concentrations of cadmium are related to dust from contaminated soil, children are not only closer to the ground, but far more likely to play in dirt and thus to have substantially higher exposures than adults. Thirdly, a recent paper by Phalen et al. (1985) showed that tracheobronchial particle deposition is generally more efficient in smaller (younger) individuals than in larger (older) people. For instance, the dose on a per kg mass basis for 5 μm diameter particles could be 6 times higher in a resting newborn than in a resting adult. Therefore, at ages when individuals are potentially more susceptible to carcinogenic damage, they may be consistly receiving higher exposures and distributing cadmium to the target site more efficiently.

For these reasons the DHS staff recommends adoption of the upper confidence limit on the unit risk, i.e. 12 excess lifetime cancer deaths per million persons.

3. Comparison of Animal- and Human-Based Risk Estimates

A comparison of the two risk assessments, one based on animal data, the other based on human data, is shown in Table IX-6 and in Figure IX-2. Comparing the low-dose risk estimates from both sets of data, it can be seen that the multi-stage model applied to lung tumors in male rats predicts about 60-fold greater excess lung cancer deaths at ambient exposure levels than a linear extrapolation from respiratory cancer deaths among the occupational cohort. The maximum likelihood animal-based estimate is about one order of magnitude larger than the upper confidence limit for the human-based estimate.

Considering the degree of uncertainty associated with extrapolation over 3-4 orders of magnitude, the differences between the two risk assessments are relatively small. Nevertheless, the ranges of risk provided by these two sources of data do not overlap. Staff members of DHS believe that the human-based risk assessment should be adopted. In reaching this decision, we have considered the following possible explanations for the difference between the two risk assessments:

(1) If the doses received by the workers were overestimated, then the potency would be underestimated by the human-based risk assessment, since the observed number of cancer deaths is fixed.

Members of DHS staff, in consultation with industrial hygiene staff of Cal/OSHA, have examined the methods used to estimate exposure levels

TABLE IX-6

ANIMAL AND HUMAN BASED PREDICTIONS

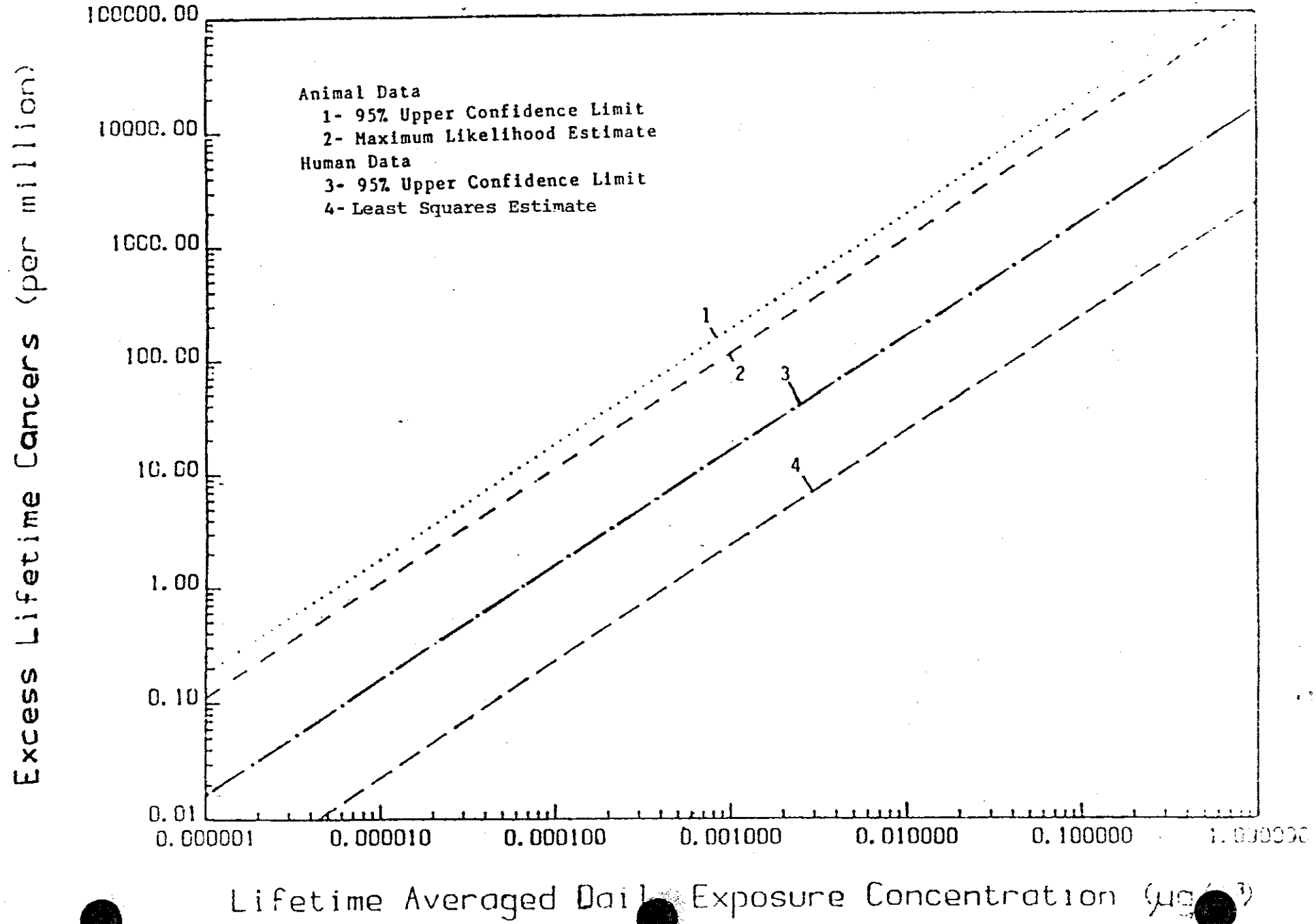
OF EXCESS LIFETIME CANCER RISKS PER MILLION PERSONS

EXPOSED TO AMBIENT AIRBORNE CONCENTRATIONS OF CADMIUM

	Ambient Air Concentration		
	1 ng/m^3	2.5 ng/m^3	40 ng/m^3
	Overall mean in California	UCL of overall California mean	hot spot mean
ANIMAL DATA			
95% Upper Confidence Limit	$180/10^6$	$450/10^6$	$7200/10^6$
Point Estimate	$110/10^6$	$275/10^6$	$4400/10^6$
HUMAN DATA			
95% Upper Confidence Limit	$12/10^6$	$30/10^6$	$480/10^6$
Point Estimate	$2/10^6$	$5/10^6$	$80/10^6$

Figure IX-2

ESTIMATES OF HUMAN EXCESS LIFETIME CANCER RISK BASED ON ANIMAL AND HUMAN DATA



reported by Thun et al. (1985), Smith et al. (1980a,b). We have concluded that the exposure levels were not likely to have been overestimated. In fact, a number of assumptions may have resulted in underestimates of past exposures. Underestimation of potency due to inaccuracies in the worker exposure data is therefore, unlikely.

(2) If the risk of respiratory cancer in cadmium-exposed workers were underestimated, then the human-based risk assessment may be too low. This could have occurred for three reasons.

The first is that the U.S. general population may not have been the most appropriate comparison population for this worker cohort. A better choice may have been the population in the state of Colorado, or perhaps that of the county where the factory was located, both of which have lower respiratory cancer mortality rates (10 to 25%) than the U.S. population (Thun et al. 1985, NIH 1975). As shown in Table IX-3, however, the use of Colorado controls did not affect the potency estimates because the model that was adopted was robust to the choice of comparison population.

The second reason that respiratory cancer risk for exposed workers could have been underestimated is that the follow-up period may have been too short to allow for the latency period. The animal studies indicated a long latency for cadmium-induced lung tumors: 23 out of 25 tumors appeared in high-dosed animals, which died after 27 months. (Had the study been terminated at 24 months, the typical length of a bioassay, these

tumors might not have been observed.) The epidemiology also indicated long latencies: 20+ years (Lemen et al. 1976) and 30+ years (Sorahan and Waterhouse 1983). Since 83% of the workers had been followed for at least 20 years and 66% had been followed for at least 30 years, the latency period for a large proportion of the lung cancers had probably passed.

The third reason that respiratory cancer risk for exposed workers could have been underestimated is if incidence and mortality differed greatly, either due to long survival with the disease, or to cure. Since lung cancer is usually fatal, having a five-year survival rate of about 10% for U.S. whites (Silverberg and Lubera 1983), it seems unlikely that the risk of respiratory cancer has been significantly underestimated because of nonfatal cases of respiratory cancer.

Because the risk estimates from the human data do not appear to be too low, the staff of DHS concludes that a significant underestimate of human carcinogenic response from cadmium exposure is not likely.

Based on examining points (1) and (2), and the fact that a linear model is likely to be health-conservative, DHS staff concludes that the estimates of human carcinogenic potencies for cadmium shown in Table IX-2 are not too low, and that the higher potency estimate derived from animal data must be explained by other arguments.

(3) If rodents and humans differ in their sensitivities to the carcinogenic effects of cadmium, then part of the discrepancy may be due to interspecies differences. These interspecies differences are likely to stem from different rates and pathways of distribution, metabolism and excretion (Williams 1978).

However, there is no evidence to suggest large differences in these processes between humans and other species (See Section V).

(4) If the conversion factor in calculating human equivalent doses from the animal bioassay were inappropriate, then the animal-based estimates of potency would be too high.

As discussed earlier in this section (IX.B.1), the interspecies conversion is based on surface area equivalence. Use of this conversion method has been justified by the argument that: (a) the metabolic rate determines the carcinogenic activity of the compound or its reactive metabolite; and (b) body surface area is related to metabolic rate.

In the case of cadmium, it could be argued that metabolic rate is not relevant since the main site of action (and the site used for these risk assessments) is the point of contact. Based on direct airborne concentrations (in $\mu g/m^3$) (averaged over lifetime), the staff of DHS recalculated the slopes of the animal-based extrapolation using the multistage model. The effect was to reduce the slope by more than one

order of magnitude, resulting in low-dose risks almost identical to those predicted by the upper confidence limit of the human-based risk estimate.

It is possible, therefore, that the discrepancy between the animal- and human-based risk assessments may be explained by an inappropriate choice of interspecies conversion factor. This issue, however, cannot be resolved given the current state of knowledge.

(5) If the greater carcinogenic response in animals were due to administration of cadmium chloride rather than the compound to which the cohort of workers was primarily exposed, cadmium oxide (Thun et al. 1985), then a direct extrapolation from the animal bioassay data would not be appropriate for ambient human exposures to cadmium oxide. A greater potency for the soluble cadmium chloride could explain the discrepancy. The pharmacologic evidence does not support this thesis, however, since animal studies indicate cadmium chloride and cadmium oxide are handled in a similar fashion by the respiratory tract (Oberdörster 1979, 1980).

(6) If the dose rate affected potency, then a lower dose rate administered over a lifetime might carry a different risk than a higher rate administered for short periods. In this case, the animals received the continuous lifetime dosing, while the workers received higher, short-term exposures. Since it does not seem likely that a lower potency would result from higher short-term exposures, dose rate probably does not explain the different risk estimates.

Members of DHS staff have concluded that the discrepancy between the animal- and human-based cadmium risk estimates is not due to deficiencies in the human data for exposure or response. Thus, reliance on the human-based risk assessment is sufficiently health-conservative because of the assumption of linearity between dose and excess relative risk. Because there may be subgroups of the population whose sensitivity to the carcinogenic effects of cadmium is greater than adult white males, and because there may be a small added risk for cancers at other sites due to cadmium exposure, the use of the upper 95% (two-tailed) confidence limit for risk is recommended. This risk is estimated at 12 excess lifetime cancer deaths per million persons continuously exposed to 1 ng/m^3 cadmium throughout their lifetimes.

C. Estimated Risks at Ambient Airborne Concentrations of Cadmium

The noncarcinogenic and carcinogenic risk assessments performed in the previous sections (IX.A and IX.B) apply to general situations. In order to estimate the hazard posed by airborne cadmium to residents of California, it is necessary to determine what the ambient concentration is. The staff of the Air Resources Board has estimated that the range of average ambient concentrations is from 1 to 2.5 ng/m^3.

As discussed in Section IX.A, lifetime exposure to an ambient airborne concentration of 1 ng/m^3 does not pose a significant hazard for renal toxicity. The ambient airborne concentration of 2.5 ng/m^3 is also two to three orders of magnitude less than the estimated ambient airborne concentration of cadmium (650 to 2500 ng/m^3) necessary to induce renal toxicity in 10 percent of the

population. Therefore, this ambient concentration is not expected to pose a significant health hazard. Since renal toxicity is believed to be the most sensitive noncarcinogenic effect caused by cadmium, no other noncarcinogenic effects are expected to occur at the present ambient levels.

The carcinogenic risk from cadmium exposure has been estimated based on the assumption that the mechanism of action is a nonthreshold process. Therefore, there is always an excess cancer risk from exposure to any level of cadmium. As discussed in Section IX.B, staff members of DHS have concluded that the best estimated range of risk for excess lifetime cancer is from 2×10^{-6} to 1.2×10^{-5} $(ng/m^3)^{-1}$. The theoretical excess lifetime cancer risk from continuous 24-hour per day exposure at the average concentrations of 2.5 ng/m^3 in California ambient air is 1 to 30 per million persons exposed (See Table IX-6).

The ARB has also identified hotspots in California where ambient exposures are 40 ng/m^3, 24-hour average. The range of estimated excess lifetime cancer risk due to the average hot spot exposures is 80 to 480 per million persons exposed. The ARB staff estimates that approximately 57,000 people in California reside in these hot spots.

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Appendix A

Carcinogenicity of Cadmium Chloride Aerosols in W Rats [1,2]

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ABSTRACT—Lung cancers were induced in inbred W rats by cadmium chloride aerosols. For 18 months, 120 male W rats were continuously exposed to cadmium chloride aerosols with cadmium (Cd) concentrations of 12.5, 25, and 50 μg/m³, respectively. For the same period of time, 41 rats were kept in filtered air; these rats served as the control group. The survivors were killed 13 months after the end of the inhalation experiments. Histopathologic examination revealed a dose-dependent incidence of primary lung carcinomas of the following types: adenocarcinomas, epidermoid (squamous cell) carcinomas, combined epidermoid carcinomas and adenocarcinomas, and mucoepidermoid carcinomas. The incidence of lung carcinomas was 71.4% in the group exposed to 50 μg Cd/m³, 52.6% in the group exposed to 25 μg Cd/m³, and 15.4% in the group exposed to 12.5 μg Cd/m³. None of the controls developed lung carcinomas. At the end of the experiment, the remaining Cd concentrations in the lungs were relatively high, almost at the same level as those in the livers.—JNCI 1983; 70:367–373.

In recent years the incidence of lung tumors has increased markedly. Air pollution is assumed to be one of the reasons for this increase (*1, 2*).

Cadmium (Cd), frequently used in industry, is highly toxic. A number of toxicity experiments revealed acute and chronic disorders in the kidneys, bones, testes, and lungs of animals exposed to Cd (*3*). Although in some of the reports a relationship between lung tumors and Cd is suggested (*4–*), it has not yet been confirmed experimentally.

A previous experiment (Oldiges H, Oberdörster G, Heering H, Hochrainer D, Mohr U: Unpublished data) in our institute and a publication by Hadley et al. (*7*) showed that 1 or 2 lung tumors developed in rats exposed to Cd aerosols. Since spontaneous, primary lung tumors seldom occur in rats, we thought these findings were important. Thus we performed a long-term inhalation experiment with cadmium chloride ($CdCl_2$) to ascertain its effects on rats.

MATERIALS AND METHODS

Inhalation system and aerosol generation.—The inhalation was performed according to a technique previously reported by Prigge and co-workers (*8, 9*) and Oberdörster et al. (*10*). The exposure took place in 225-liter inhalation chambers containing two wire mesh cages each comprised of 10 rats. We generated the aerosol by atomizing a solution of $CdCl_2$ (≈0.32 g/liter) with an ultrasonic atomizer. Since the consumption of the solution by the atomizer was 100 ml/hour, the solution was kept in a 10-liter reservoir, which was large enough for constant operation also during the weekend. The reservoir was refilled daily, except on Saturdays and Sundays, and the concentration was adjusted and checked by titration. The air flow through the atomizer was 700 liters/minute, and the droplets dried in less than 1 second. The aerosol flow through the inhalation chambers was kept at 80 liters/minute. For lower concentrations of Cd, the aerosol was diluted with filtered laboratory air. We determined the aerosol concentrations once or twice a week by drawing aerosol samples of about 1 m³ air from the intake and the exhaust of the chambers through membrane filters with a nominal pore size of 0.2 μm. Even particles smaller than this size are collected on such filters with a deposition rate of almost 100%. The mass of Cd on the filters was determined by atomic absorption spectrometry. The Cd concentrations in the chambers were assumed to be the arithmetic mean of the Cd concentrations measured simultaneously at the intake and the exhaust. The particle size distribution was measured by means of an aerosol centrifuge (*11*), where the particles were deposited on a strip of filter paper according to their aerodynamic diameter. This strip was cut into sections, and the mass of Cd on each section was determined by atomic absorption spectrometry. By the known calibration of the centrifuge, the particle size distribution could be determined. The aerodynamic mass median diameter was 0.55 μm, the arithmetic standard deviation was 0.48 μm, and the geometric standard deviation was calculated to be 1.8.

Experiment.—Male inbred W rats [TNO-W-75-SPF; i.e., from Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek (TNO), inbred Wistar 1974 (W-74), and specific pathogen-free (SPF)], purchased from F. Winkelman GmbH & Co., Borchen, Federal Republic of Germany, were used. They were approximately 6 weeks old and weighed 133–135 g at the beginning of the experiment. We divided 120 rats into 3 groups; 40 rats each were continuously (23 hr/day, 7 days/wk) exposed for 18 months to $CdCl_2$ aerosols with nominal Cd concentrations of 12.5, 25, and 50 μg/m³. (The measured concentrations and frequency of measurements are shown in table 1.) In addition, 41 rats were kept in filtered air as a control group for the same period of time. Both experimental and control animals received water ad libitum and were given a pellet diet from 4 p.m. to 8 a.m. only to minimize food contamination with

Abbreviations used: H & E=hematoxylin and eosin; NBS=National Bureau of Standards; PAS=periodic acid-Schiff; SRM=standard reference material.

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TABLE 1.—*Nominal and measured Cd concentrations of the $CdCl_2$ aerosols used for inhalation*

Nominal concentrations, $\mu g/m^3$	Measured concentrations, $\mu g/m^3$	Standard deviation, $\mu g/ml$	No. of measurements
50.0	50.8	5.9	212
25.0	25.7	3.6	220
12.5	13.4	2.1	210

$CdCl_2$. After the inhalation period, all rats were housed singly in plastic cages under conventional laboratory conditions for 13 months. During the experimental period, the animals were weighed every 3 months. Dead or dying animals were autopsied as soon as possible after they were detected. The rats surviving 31 months after the beginning of the experiment were killed by exsanguination under pentobarbital anesthesia for histopathologic examination and for measurement of the Cd content in their lungs, livers, and kidneys.

All tissues were fixed in 10% buffered Formalin. The skulls of the rats killed were decalcified in a mixture of formic acid and Formalin. The Paraplast sections (3–4 μm) for histopathologic examination were stained with H & E and by the PAS reaction.

A 0.2-g portion (wet wt) of lungs, livers, and kidneys was digested with 5 ml nitric acid (65% Suprapur; E. Merck A.G., Darmstadt, Federal Republic of Germany) under pressure at 170°C. After the removal of HNO_3, the residue was diluted to 10 ml with 1% nitric acid. NBS SRM 1577 (bovine liver; authentic Cd content: 0.27±0.04 μg/g; measured: 0.32±0.03 μg/g) was treated in the same way. The Cd concentration was determined on a Perkin-Elmer 4000 spectrometer equipped with an HGA 500 graphite atomizer and an AS 40 autosampler. The Massmann furnace was modified by the application of a L'vov platform to reduce interferences of the biological matrix and to achieve a higher sensitivity (*12–14*). For the same purpose a 5% solution of $NH_4H_2PO_4$ (E. Merck A.G.; guaranteed reagents for analysis) was added to the sample injected into the cuvette. All measurements were done in the standard addition mode.

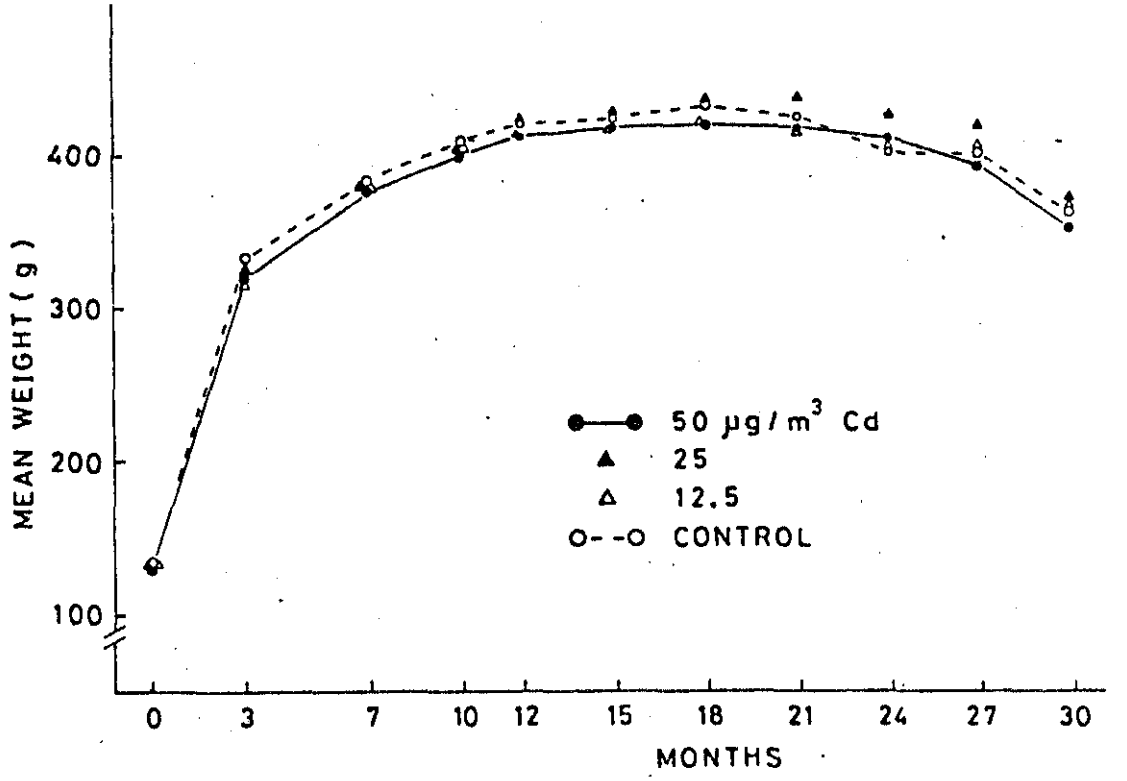
The sensitivity of the Cd determination was 1 ng Cd/ml, and the corresponding absorption value was 0.073 (absorbance of 16.6%) for a 20-μl sample.

RESULTS

During the inhalation period of 18 months, the body weights were similar among the control and the $CdCl_2$-exposed groups. Six months after the inhalation period, all rats had lost weight, which kept on decreasing until the end of the experiment. However, there were no significant differences among the 4 groups (text-fig. 1).

The mean survival times (in wk, ± SD) were 121.9±18.9, 119.2±16.9, 124.5±15.4, and 116.1±22.9 for the control group and the groups exposed to Cd at 12.5, 25, and 50 $\mu g/m^3$, respectively. The mean values include the lifetime of rats killed when the experiment was terminated. The differences were not significant, though the mean survival time of the rats exposed to 50 μg Cd/m^3 was slightly shorter than the mean survival times of the other groups (text-fig. 2).

As shown in table 2, the Cd concentrations in the lungs were 10.4 $\mu g/g$ wet weight in the highest, 4.7 $\mu g/g$ in the middle, and 5.6 $\mu g/g$ in the lowest concentration groups and less than 0.03 $\mu g/g$ in the control group. The values in the lungs and livers were comparable. The Cd concentra-



TEXT-FIGURE 1.—Average weights of rats in the indicated exposure groups.

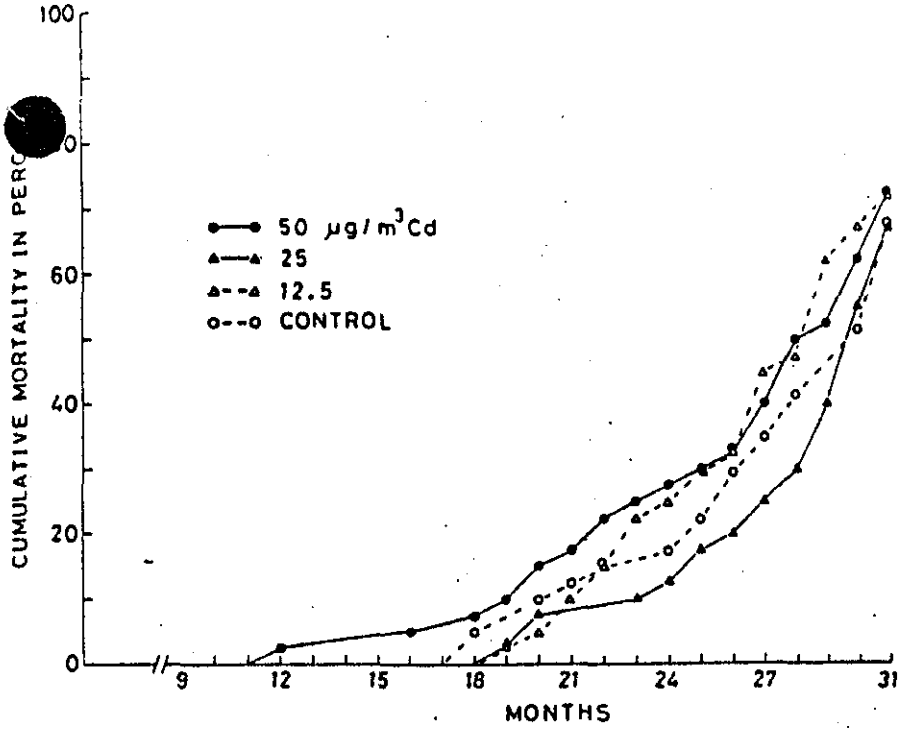


FIGURE 2.—Mortality of rats in the [illegible] exposure groups.

tions in the kidneys were about three times as high as those in the other organs examined.

The first epidermoid carcinoma occurred in a rat exposed to 25 μg Cd/m³; this rat died 20 months after the beginning of the experiment. The first adenocarcinoma was seen in a rat exposed to 12.5 μg Cd/m³; this rat died after 22 months. In 2 rats of the group exposed to 50 μg Cd/m³, which died after 23 months, a lung adenocarcinoma and lung epidermoid carcinoma, respectively, were observed.

The adenocarcinoma, mainly showing papillary and sometimes glandular structures, had developed in every lung lobe. It consisted of cuboidal and columnar cells with irregular nuclei and infrequent mitoses. In many cases mucus secretion was noted (figs. 1–3).

The epidermoid carcinoma occurred as a single tumor mass consisting of typical epidermoid structures, with or without keratinization, and frequent mitoses (figs. 4, 5).

The mucoepidermoid carcinoma showed mucus-secreting cells in the cell nests of epidermoid structures (fig. 6).

Most of the tumors were multiple. Two different types of carcinomas (adenocarcinoma and epidermoid carcinoma) occurred in the lung of 1 rat each of the groups exposed to 25 and 50 μg Cd/m³ (fig. 7).

TABLE 2.—*Concentration of Cd in lungs, livers, and kidneys of W rats exposed to $CdCl_2$ for 18 months (13 mo after the end of the inhalation)*

Exposure groups	No. of rats	Cd concentration, μg/g wet wt, in:*		
		Lungs	Livers	Kidneys
Control	9	<0.03	0.1±0.1	0.3±0.1
12.5 μg Cd/m³	6	5.6±1.0	2.2±0.6	13.5±3.2
[illegible] μg Cd/m³	9	4.7±1.5	5.9±1.5	16.4±3.6
[illegible] μg Cd/m³	9	10.4±4.2	13.5±3.0	33.6±10.7

*Results are means ± SD.

In all, primary lung carcinomas were induced in 71.4% (25/35 rats examined histopathologically) of the animals exposed to 50 μg Cd/m³, 52.6% (20/38 rats) of the animals exposed to 25 μg Cd/m³, and 15.4% (6/39 rats) of the animals exposed to 12.5 μg Cd/m³. Table 3 shows the distribution and histologic types of the tumors induced. In addition, metastases in the regional lymph nodes and kidneys and invasion into the regional lymph nodes and the hearts were observed in some of the cases. Also, several rats of the exposed groups showed lung adenomas and adenomatous hyperplasia in the bronchoalveolar area (fig. 8). The control group did not develop any lung tumors, although 2 control rats had metastases deriving from a skin epidermoid carcinoma and a skin fibrosarcoma, respectively.

Many rats in every group also showed various tumors in organs other than the lung. There were pituitary tumors (4 in the control group, 12 in the group exposed to 12.5 μg Cd/m³, 5 in the group exposed to 25 μg Cd/m³, and 1 in the group exposed to 50 μg Cd/m³), thyroid C-cell tumors (2 in the group exposed to 12.5 μg Cd/m³ and 1 in the group exposed to 25 μg Cd/m³), malignant or benign pheochromocytomas (2 in the control group), 8 in the group exposed to 12.5 μg Cd/m³, 4 in the group exposed to 25 μg Cd/m³, and 4 in the group exposed to 50 μg Cd/m³), pancreatic islet cell tumors (1 in the control group and 1 in the group exposed to 50 μg Cd/m³), testicular Leydig cell tumors (4 in the control group, 1 in the group exposed to 12.5 μg Cd/m³, 1 in the group exposed to 25 μg Cd/m³, and 2 in the group exposed to 50 μg Cd/m³), skin tumors (3 in the control group, 2 in the group exposed to 12.5 μg Cd/m³, 3 in the group exposed to 25 μg Cd/m³, and 2 in the group exposed to 50 μg Cd/m³), and systemic tumors (1 myelomonocytic leukemia in the control group, 1 histiocytoma, 1 hemangiosarcoma, and 1 malignant schwannoma in the group exposed to 12.5 μg Cd/m³, and 1 malignant lympho[illegible] in

TABLE 3.—*Lung changes in W rats after exposure to $CdCl_2$ aerosols*

Exposure groups	Initial No. of rats	No. of rats examined histologically	No. of rats with lung changes						
			Adenomatous hyperplasia	Adenoma	Total (%) carcinomas	Adenocarcinoma	Epidermoid carcinoma	Mucoepidermoid carcinoma	Combined epidermoid carcinoma and adenocarcinoma
Control	41	38[a]	1	0	0	0	0	0	0
12.5 μg Cd/m³	40	39[b]	6	1	6 (15.4)	4	2	0	0
25 μg Cd/m³	40	38[c]	5	0	20 (52.6)	15	4	0	1
50 μg Cd/m³	40	35[d]	3	1	25 (71.4)	14	7	3	1

[a] Two rats died during the first 18 mo; another rat was not examined because of autolysis.
[b] One rat was not examined because of autolysis.
[c] Two rats were not examined because of autolysis.
[d] Three rats died during the first 18 mo; 2 other rats were not examined because of autolysis.

the group exposed to 25 μg Cd/m³). In addition, many rats of the control and the $CdCl_2$-exposed groups developed chronic nephrosis, cardiac fibrosis, and testicular atrophy. The occurrence of these histopathologic findings was not significantly different among the 4 groups. The nasal cavities of rats killed at the end of the experiment had neither hyperplastic changes nor tumors.

DISCUSSION

Numerous reports concerning the occurrence of Cd in the environment and its biological and health effects have been published. Acute exposure experiments with Cd aerosols have demonstrated that Cd damages alveolar type I cells, which are then replaced by proliferated alveolar type II cells (*15–18*). Subacutely inhaled Cd aerosols enhance cell proliferation in bronchi, bonchioli, and alveoli of the exposed rats (*9*). Although parenteral administration of Cd induces tumors in rats (local sarcomas and sometimes testicular tumors), evidence of carcinogenicity of inhaled Cd has not been demonstrated (*3, 19, 20*).

In our long-term experiment, lung cancer occurred at a high incidence, and a distinct dose-response effect was seen with $CdCl_2$ (71.4% lung cancer in the highest, 52.6% in the middle, and 15.4% in the lowest Cd concentration groups; no lung cancer in the control group). Histopathologically, such typical lung tumors as epidermoid carcinomas, adenocarcinomas, combined epidermoid carcinomas and adenocarcinomas, and mucoepidermoid carcinomas were observed. Several animals showed metastases or invasion to other organs.

Our success in demonstrating Cd carcinogenicity might be due to the following two reasons: 1) We chose long-term inhalation with $CdCl_2$ aerosols. Most of the other long-term studies were performed by use of parenteral injections or peroral administration. At the end of our experiment (13 mo after the cessation of the inhalation), the retained Cd contents in the lungs were still relatively high. Probably, a relationship exists between Cd retention in the lungs and its carcinogenicity. 2) The animals were continuously observed for a long period (31 mo). In the group exposed to 50 μg Cd/m³, the first lung carcinomas were noticed 23 months after the beginning of the experiment. During the following 4 months we found no lung carcinomas; however, after the 27th month 23 lung carcinomas occurred, which means an incidence of more than 90% (only 2/25 examined rats were negative). If we had killed the animals before the 27th month, we would surely have detected initial stages of lung cancer, but not so many macroscopically and microscopically clear tumors.

As for parenteral or peroral administration of Cd, the kidney has already been proved to be the critical organ. It is estimated that a cortical Cd concentration of 200 μg/g wet weight might cause tubular dysfunction (*17*). In our experiment the average Cd concentration in the entire kidney of rats exposed to 50 μg Cd/m³ amounted to 34 μg/g wet weight. Most of the animals in both the control and $CdCl_2$-exposed groups had chronic nephrosis—obviously an age-dependent change.

The results of this experiment demonstrate that exposure to $CdCl_2$ aerosols can cause lung carcinomas. It will now be necessary to investigate the pathogenesis of this lung cancer and to evaluate the critical or lowest Cd concentration that induces lung tumors.

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Appendix B

Low dose carcinogenic risk estimation is achieved by mathematical modeling which attempts to characterize an unknown relationship between exposure and the probability of response or to place an upper bound on that probability for a given exposure. Since this relationship cannot be observed at low doses, the models are fitted to data observed at higher doses (generally by estimating the model's parameters using maximum likelihood or other statistical methods). Extrapolating the fitted equation to low doses yields the estimated risk.

The two general classes of models are; tolerance distribution and mechanistic. Both types of models are used to fit dichotomous response data: cancer vs. no cancer. Each model describes the probability of a positive response, also termed the risk, as a mathematical function of dose d, denoted P{response given d} or more simply P(d). Any model can be modified to incorporate time as a predictor variable, i.e. a time-to-tumor or temporal model describes the probability of a positive response as a function of both time and dose, P{response at or before time t given d} again abbreviated P(d,t). Note that P(d) and P(d,t) include the background rates; they are not the excess probability of cancer due to the agent, but comprise the total risk.

Tolerance distribution models are based on the concept that each individual has a tolerance or threshold level, above which a response occurs. For each model, the variability in threshold levels among individuals in the population is described by a probability distribution.

Mechanistic models are based on a presumed biological mechanism of carcinogenesis. These models assume that a tumor originates from a single cell damaged by either the agent or its metabolites.

For purposes of risk assessment, "time-to-tumor" or temporal models are generally modifications of mechanistic models. For example, the Armitage-Doll or multistage model has been modified to include a Weibull function of time, referred to in DHS documents as the "Weibullized" multistage model.

1. Probit model

This model assumes that the sensitivities of individuals in the population follow a normal distribution when plotted against the log of the dose. Thus the probit function is a tolerance distribution model which predicts that the probability of cancer can be represented as:

$$P(d) = \Phi(a + b \ln d)$$

where $\Phi(x) = \int_{-\infty}^{x} (2\pi)^{-1/2} \exp(-u^2/2)du$, the cumulative standard normal distribution.

2. Logistic model or logit model

This model associates the log of the odds (=P{response}/P{no response}) of a carcinogenic response with a linear function in the log of the dose. The natural log (ln) of the odds is known as the logit. The equation for this model in terms of the logit is:

$$\ln \frac{P(d)}{1-P(d)} = a + b \log d$$

where log can represent the logarithm base 10 or base e.

The equivalent relationship in terms of risk is:

$$P(d) = [1 + \exp(-(a + b \log d))]^{-1}$$

which has no mechanistic basis in carcinogenesis and is therefore a tolerance distribution model.

3. <u>One hit model</u>

The mechanistic interpretation of this model states that one interaction between a molecule of the carcinogenic agent and the DNA in a single cell, is sufficient to induce cancer. This interaction can be viewed as a single "hit". The statistical description states that in this model, tolerances are proportional to an exponential density in some linear function of dose:

$P(d) = 1 - \exp[-(a + bd)]$ with constraints $a \geq 0$, $b > 0$. At low doses the risk is linear in dose i.e.:

$$P(d) = a + bd.$$

Thus, $P(d)-P(0) = bd$ is the excess probability of cancer.

As indicated below, there are three models which reduce to the one-hit model for certain values of their parameters: the gamma multihit model, the multistage model, and the Weibull model. In most instances the one-hit model generates the highest risk level for a given low dose, when compared to other models, but this will not hold for all cases. For instance, if the slope of the dose response curve rises steeply through most of the observed dose range, the Weibull and multihit models will fit a supralinear curve at low doses, predicting higher risks than the one-hit model predicts (Van Ryzin 1980, Van Ryzin and Rai 1980, Van Ryzin 1982).

4. Multistage model

This model is a generalization of the one-hit model. For cancer induction to occur, a cell must undergo a series of heritable changes, in which each change or stage is a prerequisite for the next. If there are k stages and if each dose-dependent change occurs as a linear function of dose, the model can be written as:

$$P(d) = 1 - \exp[-\prod_{i=1}^{k}(a_i + b_i d)].$$

This can be written in the more generalized form

$$P(d) = 1 - \exp[-\sum_{i=1}^{k} q_i d^i] \qquad \text{with } q_i \geq 0 \text{ for all } i.$$

When $q_i = 0$ for all $i \geq 2$, the multistage model reduces to the one-hit model. At low doses, lower order terms dominate and the curve is essentially linear with $P(d) = q_1 d$.

5. Weibull model

A Weibull distribution function, also known as the extreme value function, models the probability of response in relation to a power of the independent variable. This relationship is one of direct proportionality (to the power function) near zero. When dose is the predictor, the model takes the form:

$$P(d) = 1 - \exp-(\lambda d^m) \text{ with } m>o$$

$$= 1 - \exp[-\exp(a+b \ln d)] \qquad \text{where } b=m=0 \text{ and } a=\ln \lambda.$$

When m=1, the Weibull model reduces to the one-hit model. When m>1 the low dose behavior is concave (sublinear, slope increasing) and when m<1 the low dose behavior is convex (supralinear, slope decreasing).

6. Multihit model

The gamma multihit model is also a generalization of the one-hit model where carcinogenesis results from a sufficient number, or k, "hits" in a single cell within a specific time period. If the number of hits follows a Poisson distribution, then the probability of sufficient hits to induce carcinogenesis is: $P(d) = \sum_{x=k}^{\infty} \frac{(bd)^x e^{-bd}}{x!}$ which can be shown to equal $P(d) = \sum_{x=o}^{bd} \frac{x^{k-1} e^{-x}}{(k-1)!}$.

In practice, this model is extended to include non-integer values of k, in which case $P(d) = \int_0^{bd} \frac{x^{k-1} e^{-x}}{\Gamma(k)} dx$

where $\Gamma(k)$ is the gamma function:

$$\Gamma(k) = \int_0^{\infty} e^{-t} t^{k-1} dt \qquad \text{for all } k>0$$

$$= (k-1)! \qquad \text{for k a positive integer.}$$

When k takes nonintegral values, however, the mechanistic interpretation no longer applies.

The statistical description of this model states that tolerances follow a gamma distribution with parameters $(bd)^{-1}$ and k. When k=1, the multihit model reduces to the one-hit model. When k>1 the slope at low

doses is an increasing function, and when k<1 the low dose slope is a decreasing function.

7. Time-dependent models

As described, one can model the probability of a positive response as a function of both time and dose when P(d,t) = P[response before time t, given dose d]. One procedure is to modify a mechanistic model:

$$P(d,t) = f(d)\, g(t)$$

where f(d) can be any dose response model and g(t) is a function of time. The DHS has used a modification of the multistage model:

$$P(d,t) = 1 - \exp[-(\sum_{i=0}^{k} q_i d)(t-t_\ell)^h]$$

which, at low doses, reduces to the form

$$P(d,t) = q_i d\,(t-t_\ell)^h \quad \text{where } t_\ell \text{ is the estimated latency time.}$$

Since a Weibull function of time would be $\exp(-t^h)$, the above model for P(d,t) has been termed a Weibullized multistage model.

The theoretical basis for using the Weibull function of time lies in the observation of Armitage and Doll reported in their now classical paper of 1954, that the increase in cancer incidence over a lifetime is proportional to the sixth or seventh power of age, or time since birth.

It should be noted that "time-to-tumor" is a misnomer. It is the times-to-death with tumor which are observed. In practice, the advantage of using time-dependent models is greatest when the variation in survival times is large. Since animal experiments usually end with terminal sacrifice of a large proportion of the test animals, the actual survival time of most animals is not observed, and the advantage in modeling P(d,t) is small.

Rationale for Selection of Models for Extrapolation from Animal Bioassay Data

Theoretically, a model which best describes the biological processes would be the model of choice. However, neither cancer induction and promotion, nor detoxification and DNA repair mechanisms are understood well enough to provide an explicit form for a mathematical curve relating dose to cancer risk. Empirically, several different models can be fitted to most data sets, and it is unlikely that further experimentation, even with large groups of animals, will decisively discriminate between possible models.

The choice of mathematical models to represent dose-response relationships therefore involves a substantial element of scientific judgement. The considerations for developing or selecting a risk model appropriate for low dose extrapolation include: biologic plausibility, sensitivity to the shape of the observed dose-response relationship, the degree of linearity in the low dose region, interpretability of the estimated parameters, and flexibility to take account of survival variation. The relative importance of these considerations depends on the specific data sets available.

The use of mechanistic models rather than tolerance distribution models reflects an effort to utilize as fully as possible the current knowledge on carcinogenic processes. From this point of view, the staff of DHS considers the probit and logistic models the least appropriate choices for low dose extrapolation, and the mechanistic models the most biologically plausible.

Because the staff of DHS attempts to provide health conservative estimates of low dose risk, we frequently rely on the multistage model. This is because 1) it is somewhat more flexible than the one-hit, 2) it can fit a variety of empirical data sets reasonably well, 3) it has a plausible biological basis, and 4) it has the advantage over other mechanistic models of being essentially linear at low doses.

Appendix C

Mortality Among a Cohort of U.S. Cadmium Production Workers—an Update [1]

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ABSTRACT—A previous retrospective mortality study of 292 U.S. cadmium production workers employed for a minimum of 2 years showed increased mortality from respiratory and prostate cancer and from nonmalignant lung disease. To examine further the mortality experience of these workers, investigators from the National Institute for Occupational Safety and Health extended the study to include 602 white males with at least 6 months of production work in the same plant between 1940 and 1969. Vital status was determined through 1978, which included the addition of 5 years to the original follow-up. Cause-specific mortality rates for seven causes of death potentially related to cadmium exposure were compared between the overall cohort and U.S. white males and between subgroups. Mortality from respiratory cancer and from nonmalignant gastrointestinal disease was significantly greater among the cadmium workers than would have been expected from U.S. rates. All deaths from lung cancer occurred among workers employed for 2 or more years. A statistically significant dose-response relationship was observed between lung cancer mortality and cumulative exposure to cadmium. A 50% increase in lung cancer mortality, which was not statistically significant, was observed even among workers whose cumulative exposure to cadmium was between 41 and 200 $\mu g/m^3$ over 40 years. Since the previous investigation, no new deaths from prostate cancer and no excess of deaths from nonmalignant respiratory disease have been observed.—JNCI 1985; 74:325-333.

In 1976, Lemen et al. (*1*) published the results of a study on cancer mortality among cadmium production workers at a U.S. cadmium recovery plant. Using national white male rates for comparison, Lemen et al. reported a statistically significant excess of deaths from respiratory cancer (Obs=12; SMR=235), from nonmalignant respiratory disease (Obs=8; SMR=159), and, among workers with 20 or more years since first employment, from prostate cancer (Obs=4; SMR=452). The Lemen study included only hourly workers employed for 2 or more years between January 1, 1940, and December 31, 1969, and followed these workers through 1973.

A number of previous epidemiologic and experimental studies had suggested that cadmium might cause cancer of the prostate. Two occupational reports (*2, 3*) described excess mortality from prostate cancer among cadmium workers at a small British alkaline battery plant. Cadmium, like zinc, is known to concentrate in the prostate gland (*4-5*). Numerous toxicologic studies (*6-13*) have shown that injection of cadmium metal or salts into laboratory rats produces sarcomas locally and more distant interstitial cell tumors of the testes. On the basis of these findings, the IARC (*14*) concluded in 1976 that "occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man." Substantial controversy continues, however, and although several subsequent epidemiologic studies (*15-18*) have found increased mortality from prostate cancer among occupational groups, other studies (*19-21*) have not.

Still more controversial is the possible relationship between cadmium and lung cancer. At the time of the IARC working committee, only the Lemen et al. (*1*) study had found excess mortality from respiratory cancer. Interpretation of that study was complicated because some of the long-term workers in the cohort also had been exposed to arsenic during the 1920's when the plant functioned as an arsenic smelter. Concern about the potential carcinogenicity of cadmium to the lung has increased, however, due to recent animal data. Takenaka et al. (*22*) exposed rats continuously to cadmium chloride aerosol and found a dose-dependent increase in lung tumors at exposure levels well within the current occupational limit.

Because of continuing concern about the effects of chronic cadmium exposure on mortality, NIOSH has extended the follow-up of the cohort first described by Lemen et al. (*1*). The present report describes the mortality experience of the group through 5 additional years of observation, ending December 31, 1978. In

ABBREVIATIONS USED: CI=confidence interval; Exp=expected; HIS=Health Interview Survey; IARC=International Agency for Research on Cancer; ICD=International Classification of Disease; NIOSH=National Institute for Occupational Safety and Health; NMGID=nonmalignant gastrointestinal disease; Obs=observed; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; PY=person-years; PYAR=PY at risk of dying; SMR=standardized mortality ratio(s); SRR=standardized rate ratio(s); TWA=time-weighted average.

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[3] We thank Dr. George Hutchison, Dr. Karl Shy, and Dr. Philip Enterline for their advice in the analysis and interpretation of the data, Dr. Thomas Smith for his guidance in estimating exposures, and Dr. Lynne Moody for her epidemiologic and editorial counsel. We also acknowledge the dedicated follow-up efforts of Mrs. Edith Dodd, Mrs. Clorinda Battaglia, Ms. Judy Edelbrock, Ms. Mary Hogan, and their staffs and the excellent assistance in manuscript preparation by Ms. Fran Guerra.

addition, to allow for internal comparisons, the study population was expanded to include 257 workers with brief (6–23 mo) employment and more complete ascertainment of workers with 2 or more years of employment. The total study population includes 602 white males.

BACKGROUND

The industrial plant under study has refined cadmium metals and cadmium compounds since 1925. It functioned previously as an arsenic smelter from 1918 to 1925 and as a lead smelter from 1886 to 1918. Although some cadmium processing operations were begun prior to 1925, the primary function of the plant for more than 50 years has been to recover cadmium and a number of other trace metals from "bag house" dust, a by-product of lead smelting. The facility is unusual in having a prolonged period of operation, with workers exposed predominantly to cadmium.

The industrial process recently was described by Smith et al. (*23*). Cadmium enters production principally as cadmium oxide dust (agglomerated fume). In a series of 10 physically isolated work areas, it is roasted, mixed with acid to form a cake, calcined, dissolved in water, recovered electrolytically, and treated further to produce cadmium oxide, metal, or yellow cadmium pigment. Air-monitoring data collected by the company from the 1940's to the present show that exposures differ substantially among departments and over time. Exposures have decreased over time due to the introduction of ventilation controls and to a mandatory respirator program introduced in the 1940's. Smith et al. (*23*) estimated the inhalation exposures that occurred in various departments (table 1). These estimates were based upon historical area monitoring data, adjusted to reflect the actual exposures of workers wearing respirators (*24*). Area-sampling data were first adjusted to reflect personal sampling, based on the ratio between area samples and personal exposure measurements from 1973 to 1976. For those departments and calendar periods in which workers wore respirators, the estimates of personal exposure were divided by 3.9, the geometric mean respirator protection factor measured in a survey at this plant in 1976 (*24*).

Also reflecting exposure are measurements of urine cadmium which the company obtained periodically on production workers since 1948. Urine samples were analyzed by colorimetric extraction until 1966, subsequently by atomic absorption spectroscopy. Company records contained urine cadmium measurements for 261 members (43%) of the present cohort. These data are absent or extremely sparse for workers who left employment before 1960 and are representative only of production workers employed beyond 1960. Text-figure 1 shows the distribution of the median urine cadmium levels. These urine levels suggest a highly exposed population. They provide an index of group exposure but cannot be used to measure individual exposure because of the small number of samples for most workers (median of 2 samples/person; range, 0–79).

Few data are available on exposures other than cadmium at the smelter. Small quantities of high-purity lead, arsenic, thallium, and indium are produced sporadically by a few individuals in separate buildings. Some arsenic is evolved during cadmium recovery. An industrial hygiene survey conducted by NIOSH in 1973 found 0.3 and 1.1 μg arsenic/m^3 in the pre-melt department and 1.4 μg arsenic/m^3 in the retort department (*1*). These levels are substantially below the current OSHA 10 μg/m^3 PEL time-weighted average.

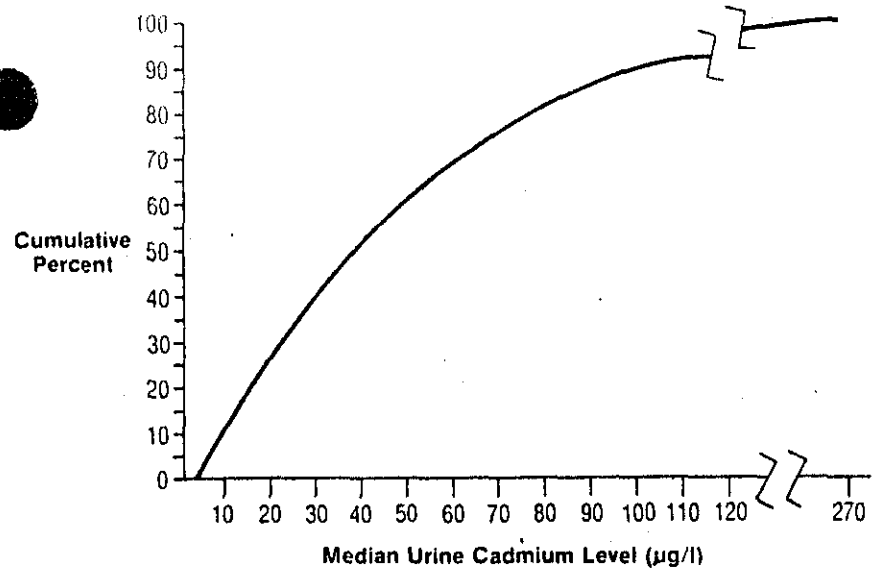
METHODS

The study population was defined from employment histories as recorded in the company personnel files. These records consist of a card for each employee and show the name, date of birth, social security number (since 1937), date of employment, date(s) of interruption of employment, and, in most cases, department or general work area for each period of employment. The records included retired and deceased as well as active employees. We enumerated all hourly employees and foremen who had worked a minimum of 6 months in a production area of the plant between January 1, 1940, and December 31, 1969. The requirement of production-area employment excluded several guards, office workers, and office area janitors who had been included in the Lemen et al. study (*1*). We also included production area foremen and a number of laborers whose records had been missing or whose employment histories had been inaccurately recorded and who thus had been omitted

TABLE 1.—*Estimates of cadmium inhalation exposures, by plant department and time period*[a]

Time period	Cadmium inhalation exposure, mg/m^3, in:									
	Plant departments:									Offices[c] and laboratories
	Sampling	Roaster	Mixing	Calcine	Solution	Tank house[b]	Foundry	Retort	Pigment	
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950–54	0.6	0.6	0.4	1.5	0.8	0.01	0.1	0.2	0.2	0.01
1955–59	0.6	0.6	0.4	1.5	0.4	0.04	0.1	0.2	0.04	0.01
1960–64	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.04	0.007
1965–76	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.04	0.007

[a] Data from Smith et al. (*23*)
[b] Tank house estimates also were used for nonproduction plant departments that were not measured directly, e.g., the repair shops.
[c] Office estimates also were used for nonplant areas that were not measured directly, e.g., areas patrolled by the plant guard.



TEXT-FIGURE 1.—Cumulative distribution of median urine cadmium levels among 261 members of the cohort with at least one urine cadmium measurement. The median urine cadmium, in micrograms/liter, was computed for each worker for whom urine samples were available.

from the Lemen cohort. NIOSH identified the cohort jointly with a representative from the company and reviewed the list with senior union officials.

For each worker, cumulative exposure to cadmium was calculated according to length of employment and jobs within the plant. Because many of the personnel records specified general work categories rather than single departments, we categorized each period of a worker's employment into one of 7 broad job categories; e.g., category 1 included production work in any of 6 "high"-exposure departments, including sampling, roasting and bag house, mixing, calcine, foundry, and retort. Category 2 included production work in the solution, tank house, and pigment departments. The average exposure to airborne cadmium for each of these composite categories was calculated on the basis of the industrial hygiene data in table 1 (*23*), with each department contributing to a weighted average according to the proportion of workers usually employed there. Each worker's cumulative exposure over time was computed as the sum of the number of days worked in a given job category multiplied by the average inhalation exposure of that category for the relevant time period. Cumulative exposure was expressed in milligram days per cubic meter (mg-days/m^3).

The vital status of all workers in the cohort was determined as of December 31, 1978. Follow-up procedures used the records of the Social Security Administration, of the state vital statistics offices, and of the company and union and direct telephoning. Death certificates were obtained for persons known to be deceased and were coded by a qualified nosologist according to the protocol of the ICD revision in effect at the time of death. The codes were subsequently converted to the seventh revision codes for the analysis (*25*). Under the rules of this and subsequent revisions, cancer is coded as the underlying cause of death if the immediate cause of death is "unmistakably a direct sequel of" the malignant disease. Deceased workers for whom no death certificate has yet been located were assumed dead on the date specified by the reporting agency, with cause of death unknown. Persons lost to follow-up were assumed to be alive—which might possibly result in overestimation of cause-specific expected deaths.

The mortality experience of the cohort was analyzed with the use of a modified life-table system developed by NIOSH (*25*). In this system, a worker accumulates PYAR upon completion of the eligibility period (in this study, at 6 months of employment). The PYAR are specific for 5-year age groups, calendar periods, and years since first employment (latency). An expected number of deaths is calculated by multiplying U.S. white male death rates by the corresponding age and calendar-year PYAR categories. The resulting quantities are summed over all ages and years to obtain the total expected numbers. The observed numbers of cause-specific deaths are compared with the numbers expected. The ratio of observed-to-expected deaths multiplied by 100 is expressed as the SMR.

In the initial analysis, in which mortality in the cadmium workers was compared to that of the general U.S. white male population, the causes for which excess mortality or morbidity were observed in previous studies of cadmium workers were considered a priori to be of particular interest. Those of central concern included deaths from prostate and lung cancers (*1*, *20*) and from nonmalignant respiratory and renal diseases (*6*, *15*, *16*). Other conditions for which a priori concern has been raised include hypertension (*6*, *26*) and renal cancer (*27*). Mortality from NMGID also was examined because of the acute gastrointestinal toxicity of cadmium and because of reports of chronic gastritis and gastrointestinal ulceration (*28–30*). Although in each case cadmium is suspected of causing an excess of mortality, we present 95% CI, corresponding to a two-sided alpha level of 0.05, throughout this paper. Where the 95% Ci includes the null but the 90% does not, we present both. CI were

TABLE 2.—*Vital status of white male cadmium production workers, by employment duration*

Worker status	Workers, No. (%) employed		
	6–23 mo	2+ yr	Total
Alive	189 (74)	222 (64)	411 (69)
Dead	60 (23)	119 (35)	179 (29)
Lost to follow-up	8 (3)	4 (1)	12 (2)
Total	257	345	602

calculated with the use of Fisher's exact CI (if either the observed or expected was less than 10) or approximate CI (if observed or expected frequencies were 10 or more) (*31*).

For selected causes of death we examined mortality in relation to cumulative exposure to cadmium. For subgroup comparisons we used the directly standardized SRR as the measure of effect (*32*). To compute these, the age-specific and calendar time-specific rates of the subgroup were multiplied by the corresponding PYAR cells of the standard population—here the PYAR distribution of the overall cadmium cohort. The results were summed to yield the expected number of deaths that would occur in the overall cohort were the rates of the subgroup to apply. This total number of expected deaths was divided by the total number of PYAR in the overall cohort to yield a directly standardized mortality rate. The ratio of this rate to the standardized rate for the overall cohort, if U.S. age, sex, race, and calendar-period rates applied, yielded the SRR.

To analyze mortality by cumulative exposure, we chose the exposure categories a priori, on the basis of current or proposed regulatory standards and on the assumption that such standards are intended to protect a worker over a 40-year working lifetime; e.g., 40 years' exposure to cadmium at or below the current NIOSH proposed TWA of 40 $\mu g/m^3$ would result in a cumulative exposure of up to 584 mg-days/m^3. Forty years' exposure to cadmium at levels above the current NIOSH TWA, but within the current OSHA 200 $\mu g/m^3$ PEL, would result in a cumulative exposure of up to 2,920 mg-days/m^3.

RESULTS

Because of the small number of nonwhites and females (total = 13) in the cohort, we restricted the analysis to the 602 white males. Table 2 shows the vital status of these workers, by duration of employment, as of December 31, 1978. Of these, 411 were alive, 179 were dead, and 12 (2.0%) had unknown vital status; 43% had been employed for less than 2 years.

Text-figure 2 shows the distribution of the cohort by year of first employment. Two-thirds of the individuals had started work before 1949 and thus could be followed beyond 30 years. Nearly 83% had over 20 years of follow-up.

Table 3 compares the number of cause-specific deaths among the overall cohort with the number expected, based on U.S. rates. A deficit was observed in mortality from all causes (SMR = 95; 95% CI = 81–110), due to a deficit in diseases of the circulatory system (SMR = 65; 95% CI = 49–85). Significantly increased mortality was observed for respiratory cancer and NMGID. The excess of nonmalignant respiratory disease was not statistically significant in the overall cohort.

Twenty deaths were due to respiratory cancer, all among workers with over 2 years' employment and all due to cancers of the lung, trachea, and bronchus. Expected deaths were 11.43 in this more specific subgroup (ICD code 162–163), which was subsequently called lung cancer. Two of the deaths from lung cancer were initially miscoded as being due to other causes. Inasmuch as the immediate causes of these 2 deaths were unmistakably direct sequels of malignant conditions, the deaths were recoded to lung cancer in accordance with the rules of the ICD Seventh Revision. Analysis that excluded these cases yielded an SMR for lung cancer of 157 (18 Obs vs. 11.43 Exp; 95% CI = 93–249; 90% CI = 102–234).

TEXT-FIGURE 2.—Cumulative distribution by year of first employment for cadmium production workers included in cohort.

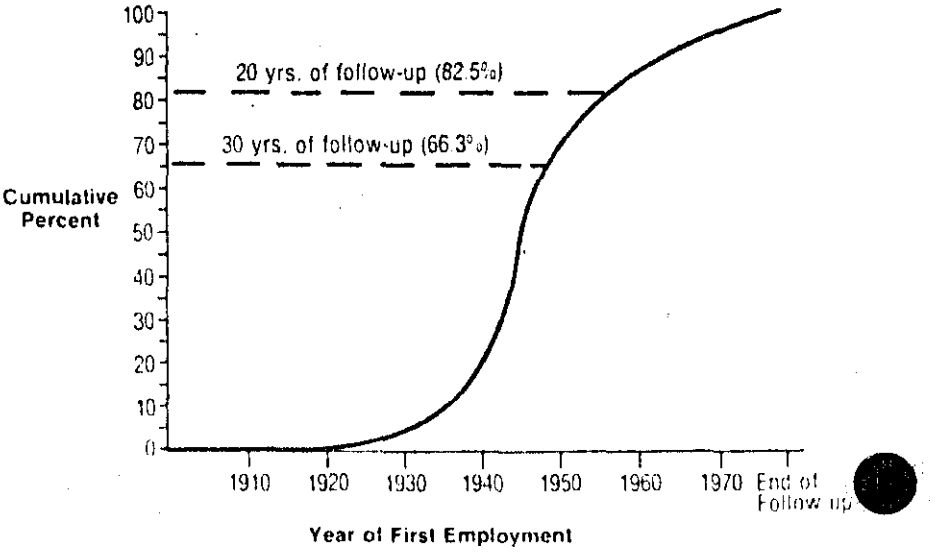


TABLE 3.—*Mortality from selected causes of death among white males with 6 or more months of cadmium production work: 1940–69*

Cause of death	ICD, 7th revision	No. of deaths		SMR	95% CI
		Obs	Exp		
Malignant neoplasm	140–199	41	36.46	112	81–153
Digestive system	150–159	7	10.85	65	26–133
Respiratory system	160–164	20	12.15	165	101–254
Genitourinary tract	177–182	6	4.45	135	49–293
Lymphatic and hematopoietic tissues	200–205	3	3.37	89	17–270
Other unspecified neoplasms		5	5.64	89	29–207
Diseases of the circulatory system: Heart disease	400–468	56	85.68	65	49–85
Nonmalignant respiratory diseases	470–493, 500–527	16	10.37	154	88–251
Acute infections, influenza, pneumonia	470–493	7	4.47	157	63–323
Other respiratory diseases	500–527	9	5.90	153	69–290
NMGID	540–543, 560–561, 570	9	2.35	383	175–727
All other causes	—	57	54.01	106	80–137
All causes of death	—	179	188.87	95	81–110

Of the 6 deaths from genitourinary cancer, 1 was due to renal cancer (vs. 0.92 Exp), 2 to cancers of the bladder and other urinary organs (vs. 1.10 Exp), and 3 to prostate cancer (vs. 2.20 Exp). No new deaths from prostate cancer were observed since the Lemen et al. report (*1*).

One of the original prostate cases was a plant guard who was excluded from this cohort because he had not worked 6 months in a production area. Another deceased worker had prostate cancer listed as a contributing cause of death but could not be included in this analysis because prostate cancer was not listed as the underlying cause of death. The remaining 3 deaths from prostate cancer had occurred among workers with 2 or more years of employment and 20 or more years of observation (vs. 1.41 Exp; SMR=213; 95% CI=44–622).

Sixteen deaths occurred due to nonmalignant respiratory disease; 7 of these involved workers employed for less than 2 years. The death certificates of 3 workers mentioned silicosis. Silica exposure may have occurred from work with refractory brick in furnace areas of the plant but is undocumented. One of the workers whose certificate mentioned advanced silicosis had been employed for only 1 year, suggesting that the exposure had occurred elsewhere.

We noted 9 deaths from NMGID, excluding cirrhosis. The death certificates of 6 of these suggested peptic ulcer disease. Most of the deaths from NMGID were of long-term employees, whereas 5 of the 6 deaths attributed to cirrhosis involved short-term workers.

No excesses were noted for deaths attributable to hypertension (3 Obs; 3.22 Exp) or to nonmalignant renal disease (1 Obs; 1.35 Exp). A single death certificate listed renal disease as the underlying cause of death [death had been due to acute nephritis (ICD code 590)], and 4 other certificates listed nonmalignant renal disease as a contributing cause of death. No comparison rates were available for analysis of these contributing causes of death.

Arsenic Exposure

Substantial arsenic exposure occurred throughout the plant during the years 1918–25 when the facility functioned as an arsenic smelter. Because arsenic is a known risk factor for lung cancer (*33*), we stratified the cohort into workers employed before and those first employed on or after January 1, 1926. We then compared mortality from lung cancer among each of these subgroups with that of U.S. white males (table 4). Lung cancer mortality was significantly elevated among persons hired prior to January 1, 1926. Among workers hired after that date, the excess of lung cancer deaths was statistically significant among workers employed for 2 or more years. When the 2 initially miscoded deaths from lung cancer are excluded from this analysis, mortality from lung cancer remains statistically above that expected both for workers hired prior to 1926 (Obs=3; Exp=0.56; 95% CI=110–1565) and for workers with 2 or more years' employment who had been hired after 1926 (Obs=15; Exp=7.0; 95% CI=120–353).

Mortality by Cumulative Exposure to Cadmium

Tables 5 and 6 present data on mortality from lung cancer and NMGID in relation to cumulative exposure to

TABLE 4.—*Mortality from lung cancer (ICD 162–163) in white male cadmium production workers, by date of hire*

Worker employment status	No. of deaths		SMR	95% CI
	Obs	Exp		
Hired prior to January 1, 1926	4	0.56	714	195–1829
Hired on or after January 1, 1926				
Overall cohort	16	10.87	147	84–239
≥2 years employment	16	7.00	229	131–371

cadmium. Only the 576 workers hired on or after January 1, 1926, are included in these analyses. Lung cancer mortality increased with increasing cumulative exposure to cadmium, and this trend was apparent both in the SRR and the SMR. A similar pattern was seen when the analysis was restricted to workers with 20 or more years since first exposure. The regression slope for the SRR for lung cancer (table 5) was 7.33×10^{-7} ($P=.0001$). The excess of deaths from lung cancer was statistically significant only for the stratum of workers whose cumulative exposure to cadmium exceeded 2,920 mg-days/m^3, the level corresponding to a 40-year exposure above the current OSHA limit (95% CI for the SMR = 113–577). In a separate analysis (not shown), workers whose cumulative exposure to cadmium ranged from 293 to 584 mg-days/m^3 showed an SMR for lung cancer of 100 and an SRR of 0.96. This level of cumulative exposure is equivalent to 40 years' exposure to airborne cadmium at levels between 21 and 40 μg/m^3. In contrast to its relationship with cumulative exposure, the excess of lung cancer mortality did not increase with length of employment beyond 2 years. Workers employed for 2–9 years, 10–19 years, and 20 or more years all showed approximately twice the number of deaths from lung cancer as expected from the U.S. rates.

Only 6 deaths from NMGID occurred among workers hired since 1926. A statistically significant upward trend was evident in the SRR when mortality from NMGID was analyzed by cumulative exposure (slope $=2.73\times10^{-7}$; $P=.014$). Because of the small number of cases of NMGID, these estimates are less stable than those for lung cancer. Three additional deaths from NMGID occurred among the 26 workers hired before 1926. If arsenic were unrelated to NMGID, these deaths would increase further the observed mortality in the high-exposure, long-term employment subgroup.

A similar analysis of deaths from nonmalignant respiratory disease was not performed, inasmuch as this study found no significant excess of deaths from this cause either in the overall cohort or among workers with 2 or more years of employment. An excess of deaths in this category was apparent, however, among workers employed for 6 months to 2 years (Obs = 8; Exp = 3.2; SMR = 249; 95% CI = 108–491). One of these deaths was attributable to silicosis.

TABLE 5.—*Lung cancer (ICD 162–163) mortality, by cumulative exposure to cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent[a]	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7,005	2	53	0.48
585–2,920[b]	41–200 μg/m^3	5,825	7	152	1.55
≥2,921	>200 μg/m^3	2,214	7	280	3.45
U.S. white males		—	—	100	1.00

[a] The TWA that over a 40-year working lifetime would result in the indicated cumulative exposure.

[b] Exclusion of the single worker hired after 1926, whose death from lung cancer was initially miscoded, reduces the number of observed deaths in this stratum to 6 and the SRR to 1.31.

TABLE 6.—*NMGID (ICD 540–43, 560.81, and 593) mortality, by cumulative exposure to airborne cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent[a]	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7,005	2	200	1.8
585–2,920	41–200 μg/m^3	5,825	1	112	1.0
≥2,921	>200 μg/m^3	2,214	3	582	11.3
U.S. white males		—	—	100	1.00

[a] The TWA that over a 40-yr working lifetime would result in the indicated cumulative exposure.

DISCUSSION

The findings of principal interest in this study were the increased mortality from lung cancer among workers employed for 2 or more years and the dose-response relationship between lung cancer mortality and cumulative exposure to cadmium. The excess of malignant respiratory disease, noted previously in this cohort by Lemen et al. (*1*), has continued during the expanded observation period. Eight new deaths from lung cancer have been identified. The excess of deaths from respiratory cancer among workers with 2 or more years of employment continues to be statistically significant (new cases = 8; Exp = 2.94; SMR = 272; 95% CI = 117–536). Furthermore, because national death rates for respiratory cancer overestimate regional (State of Colorado and Denver County) rates by 10–25% (*34*), the measured excess of lung cancer deaths among longer-term employees probably underestimates the actual increase.

The observed excess of deaths from respiratory cancer could be due to a true causal relationship between cadmium and lung cancer, to bias (the effect of uncontrolled confounding), or to chance. Cigarette smoking and exposure to arsenic are two extraneous factors which, if uncontrolled in the analysis, could explain the findings. Although the tobacco smoking habits of these cadmium workers were not recorded at the time of employment, company representatives did collect information on past tobacco use by mailing a questionnaire to members of the cohort in 1982 (*35*). Interviews with approximately 70% of survivors or next of kin showed that 77.5% of those for whom information was gathered were current or former smokers. This prevalence of "ever smokers" resembles the 72.9% prevalence noted among U.S. white males, age 20 or over, in the 1965 HIS (*36*). The 1965 HIS is perhaps the best source of information on the smoking habits of the general population during the observation period of this study. Using the 1965 survey data, one can estimate the effect that disproportionately heavy smoking by the cadmium workers would have on lung cancer mortality relative to that of the general population. Computations developed by Axelson (*37*) and Blair and Spiritas (*38*), combined with the HIS

data, show that even an assumed doubling of the proportion of heavy smokers will have only a small effect on the rate ratio for lung cancer; e.g., if 40% of the cadmium workers smoked more than 25 cigarettes/day, compared to 20% of the 1965 white male general population, the rate ratio would increase only 1.25-fold. Thus cigarette smoking alone is unlikely to account for the twofold-to-threefold increase in deaths from lung cancer observed among workers in this cohort who had had 2 or more years of employment.

Substantial and widespread arsenic exposure occurred prior to 1926 when the plant operated as an arsenic smelter. The rate of lung cancer mortality among the 26 workers employed before 1926 was nearly six times the U.S. rates. Even after 1925, a small and unspecified number of workers occasionally processed arsenic in one area of the plant. This was an intermittent operation, apparently staffed by workers from the roasting area, and lasted into the 1930's. A second and continuing source of exposure involved workers in the sampling, mixing, roasting, and calcine furnace areas of the plant who were exposed to arsenic contamination from the incoming feed material. Only six industrial hygiene measurements were made in these areas before 1975. In 1950, airborne arsenic concentrations ranged from 300 to 700 $\mu g/m^3$ near the roasting and calcine furnaces, the areas of highest exposure. Measurements by the company and OSHA in 1979 show that arsenic exposures in these areas had decreased to about 100 $\mu g/m^3$. Although air levels of arsenic in this confined area were still 10 times higher than the legal OSHA threshold limit value of 10 $\mu g/m^3$, actual personal exposures were lower due to respirator usage. One can estimate the number of lung cancer deaths potentially attributable to arsenic by assuming *a*) an average airborne arsenic exposure of 500 $\mu g/m^3$ in the "high-arsenic" work areas during the years of this study, *b*) a respirator protection factor of 75% (similar to that assumed for cadmium), and *c*) an estimated 20% of PY of exposure spent in high-arsenic jobs, an estimate based on personnel and biologic monitoring data. On the basis of these assumptions, the average airborne arsenic exposure of persons in this study would have been 25 $\mu g/m^3$. Inasmuch as the 576 workers hired after 1926 were employed an average of 3 years, they acquired 1,728 PY of exposure to 25 $\mu g/m^3$. Such an exposure should result in no more than 0.77 lung cancers, on the basis of a risk assessment model for arsenic developed by the OSHA (*39*).

Although the estimate of an average air exposure to arsenic of 25 $\mu g/m^3$ rests on several assumptions, it is more likely to overestimate than to underestimate actual exposures. Only a fraction of jobs in the high-arsenic areas involved exposures as high as those of the furnace areas. High-exposure jobs in the roaster area were frequently staffed by entry-level workers, many of whom worked less than 6 months. These very short-term workers with brief but high exposure were excluded from the mortality study, yet they were included in our estimate of 20% of PY of exposure spent in high-arsenic jobs. In addition, urinary arsenic levels measured on workers in the high arsenic areas from 1960 to 1980 averaged only 46 μg/liter, a level consistent with an average inhaled arsenic concentration of 14 $\mu g/m^3$ (*40*). Thus the assumption of an average inhaled concentration of 125 $\mu g/m^3$ (25% of 500 $\mu g/m^3$) over these years overestimates the actual exposures by ninefold, more than compensating for the unquantified higher exposures during the early years. Arsenic alone does not appear to explain the observed excess of deaths from lung cancer.

The central finding of the study was the observed dose-response relationship between mortality from lung cancer and cumulative exposure to cadmium. Previous epidemiologic studies of cadmium workers have had insufficient industrial hygiene data to estimate cumulative exposure. The strong dose-response pattern observed in this study is consistent with a causal relationship between cadmium and lung cancer. It also suggests that the current OSHA occupational standard, limiting exposure to cadmium dust to 200 $\mu g/m^3$, is inadequate to protect workers over a 40-year working lifetime. Workers whose cumulative exposure was below the 40-year equivalent of the NIOSH-recommended TWA of 40 $\mu g/m^3$ showed no excess of lung cancer deaths, whereas workers whose cumulative exposure was within the current OSHA limit but above the NIOSH recommended limit showed a 50% excess in lung cancer deaths.

The potential role of cadmium as a pulmonary carcinogen has gained biologic plausibility because of the experimental induction of lung cancer in rats exposed to cadmium chloride aerosol (*22*). Epidemiologic studies of mortality among cadmium workers in England and Sweden have, however, shown conflicting results. Sorahan and Waterhouse (*18*) found a statistically significant excess of deaths from respiratory cancer (Obs=89; Exp=70.2; SMR=127; 90% CI=106-151) in a cohort of 3,025 English nickel-cadmium battery workers. A subset of these workers had been included in the earlier studies of Potts (*2*) and Kipling and Waterhouse (*3*). Although the authors observed a positive association between death from respiratory cancer and cumulative duration of employment in jobs with high or moderate exposure to cadmium, they noted that these workers also were exposed potentially to oxyacetylene welding fumes and to nickel hydroxide dust. Holden (*17*) found a statistically significant excess of deaths from respiratory cancer (Obs=36; Exp=26.06; SMR=138; 95% CI=108-339) and from prostate cancer (Obs=8; Exp=3.00; SMR=267; 90% CI=115-525) among 624 cadmium "vicinity" workers but not among 347 workers employed directly in manufacturing cadmium copper alloys. The vicinity workers were also exposed to arsenic.

Armstrong and Kazantzis (*19*), excluding the cohorts studied by Sorahan and Waterhouse (*18*) and Holden (*17*), recently described mortality among workers enrolled in the registry of English cadmium workers. A small, statistically insignificant excess of deaths from respiratory cancer was evident in the overall cohort (Obs=199; Exp=185.6; SMR=107; 95% CI=92-122). This marginal excess is consistent with the results in our study, inasmuch as most of the workers in the Armstrong cohort

had only minimal exposure to cadmium. Less than 3% of the workers in the Armstrong cohort were classified as "ever highly exposed." High exposure was defined as having worked at least 1 year in a job that the authors judged would produce a urine cadmium level of at least 20 μg/liter following chronic exposure. In our cohort, 81% of workers for whom urine cadmium had been measured had a median urine cadmium of at least 20 μg/liter. Even among workers with less than 2 years of employment, approximately 30% had a median urine level of 20 μg/liter. One might argue that in each of the epidemiologic studies in which excess mortality from lung cancer was seen, other occupational exposures such as arsenic or nickel were present and could have contributed to the problem. Unfortunately, the published versions of these studies do not include sufficient information on the level of exposure to either cadmium or to other metals to permit assessment of this problem.

Increased mortality from NMGID has not been reported previously in association with cadmium. Ingested cadmium is a severe gastrointestinal irritant in man (*5*, *28*), and Tsuji et al. (*29*) and Adams et al. (*30*) have commented on the frequent observation of gastritis and gastrointestinal ulceration among chronically exposed persons. In our study we observed a 2.8-fold overall increase in deaths from NMGID (excluding cirrhosis of the liver) among workers employed on or after January 1, 1926. Deaths from these causes showed a general association with prolonged employment. Because NMGID previously has not been examined systematically, we view this finding as a hypothesis to be examined further in future studies rather than as a definitive conclusion.

No new deaths from prostate cancer have occurred in this cohort since the Lemen study (*1*). In addition, 1 of the 4 original cases was excluded from this analysis because of the revised definition of the cohort. The excluded worker had been employed for 13 years as a guard who patrolled the entire plant but at no time had worked for 6 months in a production area. Exclusion of such a worker is to a certain extent arbitrary. Also, because the small size and short additional follow-up of this cohort has low statistical power, and because prostate cancer is frequently a nonfatal disease imperfectly studied by death certificate data, we believe that the absence of new cases during the 5 additional years of follow-up weakens but does not refute the possible association between cadmium and prostate cancer.

The presence of only 1 death attributed to chronic renal failure is interesting, inasmuch as cadmium is a known nephrotoxin and because increased mortality from chronic nephritis and nephrosis has been noted among Swedish battery workers (*15*, *16*). The difference may well be due to local differences in recording certain types of information on death certificates. The comparisons in our study were based upon the underlying causes of death and ignore the data for 4 individuals for whom renal disease was noted as a contributing cause of death. Impaired renal function frequently is underreported on death certificates, even when the disease was sufficiently severe to require chronic hemodialysis (*41*).

In contrast to the Lemen study (*1*), we found no excess of deaths from nonmalignant respiratory disease either in the overall cohort or among workers with 2 or more years of employment. If deaths from silicosis are excluded, the only increase in mortality from these causes is among workers with short-term employment. The significance of this finding is unclear.

In summary, the finding of increased lung cancer mortality in this follow-up analysis is consistent 1) with the previous mortality study of this cohort (*1*), 2) with the recently published rat inhalation study (*13*), and 3) with the epidemiologic findings of Sorahan and Waterhouse (*18*). An association of cadmium with NMGID was also observed. Previous findings (*1–3*) of prostate cancer among exposed workers were somewhat weakened.

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Appendix D

Appendix D

The construction of life tables is described in detail by Chiang (1984). The abridged life table uses age intervals larger than one year (in this case, five-year age intervals). The data collected from vital statistics are:

m_i = annual death rate for age interval i

ℓ_i = annual lung cancer death rate for age interval i

The life table is constructed by calculating the following:

(1) The probability of dying in the i^{th} age interval, given survival to the beginning of that interval:

$$q_i = 1-\exp(-5 \cdot m_i)$$

(2) The probability of surviving the i^{th} age interval, given survival to the beginning of that interval:

$$p_i = 1-q_i$$

(3) The cumulative probability of surviving to the beginning of the i^{th} age interval:

$$c_i = p_1 \cdot p_2 \cdots p_{i-1} = \prod_{j=1}^{i-1} p_j$$

(4) The probability of dying of lung cancer in the i^{th} interval, given survival to the beginning of that interval:

$$p\ell_i = (\ell_i/m_i) \cdot q_i$$

(5) The unconditional probability of dying of lung cancer in the i^{th} interval, (i.e. not conditioned on surviving to the beginning of the interval) is

$$p\ell_i \cdot c_i$$

(6) The cumulative probability of dying of lung cancer through the end of the i^{th} interval:

$$c\ell_i = p\ell_1 c_1 + p\ell_2 c_2 + \cdots + p\ell_i c_i = \sum_{j=1}^{i} p\ell_j c_j$$

The life table for an exposed population is constructed in an identical manner such that only the data for the age-specific lung cancer death rates are modified. (This also changes the age-specific overall death rates.) The lung cancer death rates (ℓ_i) for an exposed population are derived by adding the observed rates in an unexposed population to the excess rates predicted by the model. The overall death rates (m_i) are obtained by adding the observed nonlung cancer death rates to the predicted lung cancer death rates. From these values, a new life table is constructed.

The cumulative probability of a lung cancer death for the last age interval in an exposed population is then compared to the same probability in an unexposed population. The difference between the two is the excess lung cancer death rate due to exposure.

TABLE D-1a

LIFE TABLE FOR CALIF MALES
BACKGROUND : LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034558	0.982854	1.00000	0.000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98285	0.000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.000015	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.000036	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983481	0.93185	0.000214	0.0010611	0.0009888	0.0012286
10	45	0.0053525	0.973592	0.91646	0.000456	0.0022498	0.0020618	0.0032904
11	50	0.0082844	0.959424	0.89225	0.000933	0.0045697	0.0040773	0.0073677
12	55	0.0129362	0.937366	0.85605	0.001496	0.0072432	0.0062006	0.0135683
13	60	0.0199206	0.905197	0.80243	0.002312	0.0110029	0.0088291	0.0223974
14	65	0.0309841	0.856483	0.72635	0.003265	0.0151233	0.0109850	0.0333824
15	70	0.0466398	0.792036	0.62212	0.004359	0.0194407	0.0120944	0.0454768
16	75	0.0701389	0.704199	0.49274	0.004803	0.0202560	0.0099809	0.0554577

TABLE D-1b

LIFE TABLE FOR CALIF FEMALES
BACKGROUND : LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98659	0.000005	0.00002498	0.00002465	0.0000246
3	10	0.0002384	0.998809	0.98539	0.000000	0.00000000	0.00000000	0.0000246
4	15	0.0005583	0.997212	0.98422	0.000002	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.000002	0.00000998	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97846	0.000002	0.00000998	0.00000977	0.0000540
7	30	0.0008328	0.995845	0.97494	0.000015	0.00007484	0.00007297	0.0001270
8	35	0.0012411	0.993814	0.97089	0.000039	0.00019440	0.00018874	0.0003157
9	40	0.0020251	0.989925	0.96488	0.000113	0.00056215	0.00054241	0.0008582
10	45	0.0030578	0.984827	0.95516	0.000244	0.00121072	0.00115643	0.0020146
11	50	0.0048217	0.976180	0.94057	0.000462	0.00228238	0.00214695	0.0041615
12	55	0.0072160	0.964553	0.91826	0.000738	0.00362423	0.00332798	0.0074895
13	60	0.0112514	0.945296	0.88572	0.001011	0.00491544	0.00435370	0.0118432
14	65	0.0168356	0.919268	0.83727	0.001212	0.00581195	0.00486615	0.0167094
15	70	0.0263732	0.876458	0.76967	0.001305	0.00611309	0.00470507	0.0214144
16	75	0.0405130	0.816633	0.67459	0.001126	0.00509641	0.00343796	0.0248524

TABLE D-2a

LIFE TABLE FOR CALIF MALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034568	0.982854	1.00000	0.00000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98286	0.00000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.00000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.00000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.00000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.00000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.00001500	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.00003600	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983491	0.93185	0.00021401	0.0010612	0.0009888	0.0012286
10	45	0.0053525	0.973592	0.91646	0.00045601	0.0022498	0.0020619	0.0032905
11	50	0.0092845	0.959424	0.89225	0.00093303	0.0045699	0.0040775	0.0073680
12	55	0.0129363	0.937366	0.85605	0.00149605	0.0072435	0.0062008	0.0135688
13	60	0.0199207	0.905196	0.80243	0.00231209	0.0110034	0.0088295	0.0223982
14	65	0.0309842	0.856483	0.72636	0.00326514	0.0151239	0.0109854	0.0333836
15	70	0.0466300	0.792035	0.62211	0.00435920	0.0194416	0.0120949	0.0454785
16	75	0.0701392	0.704198	0.49274	0.00480323	0.0202570	0.0099813	0.0554599

TABLE D-2b

LIFE TABLE FOR CALIF FEMALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.00000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98659	0.00000500	0.00002499	0.00002465	0.0000246
3	10	0.0002384	0.998809	0.98539	0.00000000	0.00000000	0.00000000	0.0000246
4	15	0.0005584	0.997212	0.98422	0.00000200	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.00000200	0.00000998	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97846	0.00000200	0.00000998	0.00000977	0.0000540
7	30	0.0008328	0.995845	0.97494	0.00001500	0.00007485	0.00007297	0.0001270
8	35	0.0012411	0.993814	0.97093	0.00003900	0.00019440	0.00018874	0.0003158
9	40	0.0020251	0.989925	0.96489	0.00011300	0.00056216	0.00054242	0.0008582
10	45	0.0030578	0.984827	0.95516	0.00024401	0.00121076	0.00115646	0.0020146
11	50	0.0048217	0.976180	0.94057	0.00046202	0.00228245	0.00214702	0.0041617
12	55	0.0072160	0.964563	0.91826	0.00073803	0.00362436	0.00332809	0.0074898
13	60	0.0112515	0.945296	0.88572	0.00101104	0.00491563	0.00435386	0.0118436
14	65	0.0168356	0.919267	0.83727	0.00121205	0.00581219	0.00486635	0.0167100
15	70	0.0263733	0.876458	0.76967	0.00130506	0.00611336	0.00470528	0.0214152
16	75	0.0405131	0.816633	0.67459	0.00112605	0.00509665	0.00343812	0.0248534

TABLE D-3a

LIFE TABLE FOR CALIF MALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
UPPER CONFIDENCE LIMIT - LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034558	0.982864	1.00000	0.00000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98285	0.00000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.00000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.00000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.00000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.00000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.00001500	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.00003601	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983480	0.93185	0.00021404	0.0010613	0.0009890	0.0012288
10	45	0.0053526	0.973592	0.91646	0.00045609	0.0022502	0.0020622	0.0032911
11	50	0.0092847	0.959423	0.89225	0.00093321	0.0045708	0.0040783	0.0073693
12	55	0.0129356	0.937365	0.85605	0.00149638	0.0072450	0.0062021	0.0135714
13	60	0.0199212	0.905194	0.80243	0.00231263	0.0110059	0.0088315	0.0224029
14	65	0.0309850	0.856479	0.72635	0.00326597	0.0151277	0.0109881	0.0333911
15	70	0.0466312	0.792030	0.62211	0.00436038	0.0194468	0.0120980	0.0454891
16	75	0.0701406	0.704193	0.49273	0.00480463	0.0202628	0.0099840	0.0554731

TABLE D-3b

LIFE TABLE FOR CALIF FEMALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
UPPER CONFIDENCE LIMIT - LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.00000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98658	0.00000500	0.00002499	0.00002465	0.0000247
3	10	0.0002384	0.998809	0.98539	0.00000000	0.00000000	0.00000000	0.0000247
4	15	0.0005584	0.997212	0.98422	0.00000200	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.00000200	0.00000999	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97845	0.00000200	0.00000998	0.00000977	0.0000540
7	30	0.0006328	0.996845	0.97494	0.00001500	0.00007485	0.00007298	0.0001270
8	35	0.0012411	0.993813	0.97089	0.00003901	0.00019443	0.00018877	0.0003158
9	40	0.0020252	0.989925	0.96489	0.00011302	0.00056225	0.00054251	0.0008583
10	45	0.0030579	0.984827	0.95516	0.00024405	0.00121097	0.00115667	0.0020150
11	50	0.0048218	0.976179	0.94066	0.00046211	0.00228290	0.00214745	0.0041624
12	55	0.0072162	0.964562	0.91826	0.00073819	0.00362514	0.00332881	0.0074912
13	60	0.0112517	0.945295	0.88572	0.00101128	0.00491678	0.00435488	0.0118461
14	65	0.0166359	0.919266	0.83726	0.00121236	0.00581366	0.00486757	0 0167137
15	70	0.0263737	0.876456	0.76967	0.00130541	0.00611502	0.00470654	0.0214202
16	75	0.0405134	0.816632	0.67458	0.00112638	0.00509813	0.00343910	0.0248593

TABLE D-4a

LIFE TABLE FOR CALIF MALES - 10 YR LAGGED CUMULATIVE DOSE
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034568	0.982854	1.00000	0.00000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98286	0.00000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.00000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.00000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.00000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.00000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989854	0.95240	0.00001500	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.00003600	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983481	0.93185	0.00021400	0.0010612	0.0009888	0.0012286
10	45	0.0053525	0.973592	0.91646	0.00045601	0.0022498	0.0020619	0.0032905
11	50	0.0082845	0.959424	0.89225	0.00093302	0.0045698	0.0040774	0.0073679
12	55	0.0129363	0.937366	0.85605	0.00149604	0.0072434	0.0062007	0.0135687
13	60	0.0199206	0.905197	0.80243	0.00231208	0.0110033	0.0088294	0.0223981
14	65	0.0309842	0.856483	0.72636	0.00326512	0.0151238	0.0109853	0.0333834
15	70	0.0466299	0.792035	0.62211	0.00435917	0.0194415	0.0120948	0.0454782
16	75	0.0701391	0.704198	0.49274	0.00480320	0.0202568	0.0099813	0.0554595

TABLE D-4b

LIFE TABLE FOR CALIF FEMALES - 10 YR LAGGED CUMULATIVE DOSE
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.00000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98658	0.00000500	0.00002498	0.00002465	0.0000246
3	10	0.0002384	0.998809	0.98539	0.00000000	0.00000000	0.00000000	0.0000246
4	15	0.0005584	0.997212	0.98422	0.00000200	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.00000200	0.00000998	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97846	0.00000200	0.00000998	0.00000977	0.0000540
7	30	0.0008328	0.995845	0.97494	0.00001500	0.00007485	0.00007297	0.0001270
8	35	0.0012411	0.993814	0.97089	0.00003900	0.00019440	0.00018874	0.0003158
9	40	0.0020251	0.989925	0.96483	0.00011300	0.00056216	0.00054242	0.0008582
10	45	0.0030578	0.984827	0.95516	0.00024401	0.00121075	0.00115646	0.0020146
11	50	0.0048217	0.976180	0.94067	0.00046201	0.00228244	0.00214701	0.0041616
12	55	0.0072160	0.964563	0.91826	0.00073802	0.00362433	0.00332807	0.0074897
13	60	0.0112515	0.945296	0.88572	0.00101103	0.00491560	0.00435384	0.0118435
14	65	0.0166356	0.919268	0.83727	0.00121204	0.00581216	0.00486632	0.0167099
15	70	0.0263733	0.876458	0.76967	0.00130505	0.00611333	0.00470525	0.0214151
16	75	0.0405130	0.816633	0.67458	0.00112605	0.00509662	0.00343810	0.0248532

TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CADMIUM

PART C - PUBLIC COMMENTS AND RESPONSES

December 1986

Southern California Edison Company

P O BOX 800

2244 WALNUT GROVE AVENUE

ROSEMEAD CALIFORNIA 91770

EDWARD J FAEDER Ph D
MANAGER OF ENVIRONMENTAL OPERATIONS

TELEPHONE
(818) 302-2009

January 21, 1986

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
Attention: Cadmium
P. O. Box 2815
Sacramento, California 95812

Dear Mr. Loscutoff:

SUBJECT: Draft Report to the Scientific Review Panel on Cadmium

Southern California Edison Company has reviewed the draft document entitled "Report to the Scientific Review Panel on Cadmium" and would like to submit these brief comments on several important issues which are addressed in this report. The issues of primary concern are the cadmium emission estimates from oil-fired power plants and the methods used to estimate the carcinogenic risks from cadmium.

In addition we would like to submit for your information the transcripts from the recent U.S. Environmental Protection Agency's public hearing on the EPA Notice of Intent to List Cadmium Under Section 112 of the Clean Air Act.

Edison regrets that we were unable to meet the stringent deadline for comment submittal. We believe, however, that the time provided for public review, which has been on the order of two weeks, is not sufficient to allow the level of review and comment these important documents require.

THE ABOVE MENTIONED ATTACHMENT OF TRANSCRIPTS OF EPA HEARING ON NOTICE OF INTENT TO LIST CADMIUM UNDER SECTION 112 OF THE CLEAN AIR ACT CAN BE FOUND AS APPENDIX F OF COMMENTS FROM THE CADMIUM COUNCIL.

EMISSION ESTIMATES

ARB has estimated cadmium emission factors (lb of Cd per lb of fuel burned) from oil-fired power plants by taking an average of estimates from two studies, Taback et al. (1979) and Krishnan and Hellwig (1982). The estimated emission factor was then applied to the residual fuel oil consumption by utilities in 1983 to obtain the emission estimate.

Taback et al. analyzed flue gas particulate samples from oil fired power plants in the South Coast Air Basin. Estimates of cadmium emissions were made for four of the tests. Since total fuel oil consumption was recorded during these tests, it is possible to calculate fuel oil concentration of cadmium. This data is presented in Table 1.

TABLE 1. Cadmium Emission Estimates Based on Stack Sampling. (Taback et al. 1979)

TEST#	Emission Rate (lb/hr)	Fuel Oil Consumption Rate (lb/hr)	Calculated Fuel Oil Concentration
11	0.01	218,765	0.0457 ppm
12	< 0.1	220,497	< 0.453 ppm
32	< 0.1	210,857	< 0.474 ppm
33	0.08	209,055	0.383 ppm

Krishnan and Hellwig (1982) have estimated emissions from residual oil-fired boilers equipped with various types of control devices. Emission estimates are given in terms of picograms per joule of energy content in the fuel. ARB has assumed an energy content of fuel oil of 152,000 Btu/gallon which is equivalent to 1.6×10^8 joules/gallon. It is possible to calculate the concentration of cadmium in fuel oil which would produce the estimated emissions. This is shown in Table 2.

TABLE 2. Cadmium Emission Estimates from Krishnan and Hellwig (1982).

Boiler Type/ Control Device	Emission Rate (pg/J)	Equivalent* Concentration In Oil
Utility/ No Controls.	71.8	3.20 ppm
Utility/ Electrostatic Precipitator	14.4	0.642 ppm

* Cadmium concentration in fuel oil which would give equivalent stack emissions (assumes no control device).

ARB has estimated an average emission factor of approximately 3.67×10^{-6} lb/gal or 0.46 ppm in fuel oil. This was apparently obtained by averaging (1) the highest identified emission rate from the Taback study (and excluding the other measured value which was about 10 times lower) and; (2) the estimate from the Krishnan study which applies to utility boilers with ESP control (even though utility boilers in California are not equipped with these devices).

Edison has measured cadmium concentrations in fuel oil at two power plants and has found an average concentration of approximately 0.1 ppm. There is a great range in trace element concentrations in crude and fuel oils and "typical" concentration estimates may be significantly different from measured values at a specific plant. If the two measured values obtained by Taback *et al.* are averaged (the "less than" values are excluded) a fuel concentration of 0.21 ppm is obtained and this agrees fairly well with the Edison data.

The emissions estimates presented by Krishnan and Hellwig should be viewed very cautiously. Although several studies of trace element emissions are cited by the authors, there is no specific reference for the data or methods used to calculate emissions of cadmium and other trace elements from oil-fired power plants. Thus the emissions factors are essentially unreferenced. The authors also point out that the emission factors are "only general estimators of the actual emissions and could vary widely from plant to plant".

In view of the shortcomings of the Krishnan and Hellwig emissions factors and the fact that they are not in agreement with measured power plant emissions and fuel oil concentrations obtained at California plants, it would be preferable to use the data from Taback et al. in estimating cadmium emissions from residual oil-fired power plants. It must be recognized that emissions at any specific facility could be lower and that the emission factor is only an estimate.

The ARB's emissions estimates for residual fuel oil-fired power plants should be recalculated using the data from Taback et al. and excluding the emissions factors from Krishnan and Hellwig which are not in good agreement with data from California power plants.

EVALUATION OF THE CARCINOGENIC RISKS OF CADMIUM

In June of 1985, the U.S. Environmental Protection Agency released a final report addressing the mutagenicity and carcinogenicity assessment of cadmium. In this report EPA states:

> "Altogether, the epidemiologic data appear to provide limited evidence of lung cancer risk from exposure to cadmium, based on the IARC classification system...and the U.S. Environmental Protection Agency's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984)".

IARC has described "limited evidence" as "evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded". EPA derived a unit risk estimate for cadmium of 1.8×10^{-3} using the data from a study by Thun et al. (1985).

DHS, after evaluating the same study by Thun et al., has concluded that "there is sufficient evidence for carcinogenicity in humans." DHS has also concluded that the range of unit risk estimates for cadmium is from 2.3×10^{-3} to 21×10^{-3}. The upper limit of this range is more than 10 times higher than the unit risk recommended by EPA.

Questions therefore arise with respect to: (1) Why does the DHS interpretation of the data differ both qualitatively and quantitatively from the interpretation of EPA?, and (2) How strong is the evidence that cadmium is a human carcinogen?

Risk estimates developed by both EPA and DHS are shown in Table 3.

TABLE 3. Comparison of Unit Risk Estimates for Cadmium Derived by DHS and EPA.

SOURCE	UPPER LIMIT	BEST ESTIMATE	LOW ESTIMATE
EPA	3.5×10^{-3}	1.8×10^{-3}	not calculated
DHS (uncorrected)	18×10^{-3}	2.0×10^{-3}	1.6×10^{-5}
DHS (corrected for CdO)	21×10^{-3}	2.3×10^{-3}	1.8×10^{-5}

It should be noted that although EPA calculated a 95% upper confidence limit (UCL) for cadmium potency, this was not suggested as the best estimate of potency. EPA felt that the 95% UCL was "an unnecessary added level of conservatism, since the model used already inflates the risk estimate if nonlinear components exist or confounding factors are present". [EPA 1985]

One minor reason for the differences between the EPA and DHS risk estimates is that DHS has corrected exposures on the assumption that the cadmium levels in the Thun et al. paper were reported as cadmium oxide. In fact, the values reported by Thun were reported as cadmium (not the oxide) and this adjustment was incorrect. The last line of Table 1 should therefore be disregarded and these values deleted from the draft report.

The best estimates derived by EPA and DHS are quite similar (2.0×10^{-3} versus 1.8×10^{-3}) in spite of the fact that they are using different models and that DHS has censored the data from the study by excluding any data which does not show an increased cancer risk from cadmium exposure, as discussed below.

The significant differences between the DHS and EPA estimates result from the methods used to calculate upper limits of risk. EPA has used a statistical approach to derive a probabilistic estimate of the upper limit of risk. DHS has used a technique which they refer to as "maximizing the slope" which is not really a model but merely a sensitivity analysis using "worst case" assumptions to derive a non-statistical "worst case" estimate of risk. DHS has derived an upper limit by assuming; (1) that the entire moderate exposure group was exposed to the lowest level of the concentration interval for that group; and (2) that the true cancer response observed in that group may have been higher (i.e. the 95% UCL for the relative risk). DHS also uses a higher estimate of the background rate for lung cancer than is used by EPA in their assessment.

The combined effect of these assumptions is to create a "worst case" estimate of risk which probably has no bearing on the true risk.

The major problem with the model used by DHS is that it cannot accommodate data which indicate no increase in cancer among the exposed population. The low exposure group in the Thun et al. study is a case in point. This data was excluded from the analysis because it did not fit into the model used by DHS and because DHS staff did not "believe" that cadmium exposure could have a health protective effect. In calculating the minimized estimate of the slope for the moderate exposure group, another data point was deleted for the same reasons. This type of data censoring is clearly unscientific. No reasonable justification has been given for this selective use of data. The data for the low exposure group is just as valid as the other data presented in the study. If the model chosen by DHS does not allow for the use of all the data available in the study, then a different model should be chosen. This would be preferable to exclusion of data based on a priori assumptions concerning the shape of the dose response curve. Other models, such as the one used by EPA, do not present this type of problem. Models which allow for the use of all the data should be used by DHS.

The issue of thresholds has not been dealt with adequately in the DHS report. The lack of response of the low exposure group in the Thun study should have stimulated some discussion with regard to the possibility of a threshold phenomenon. This is particularly true in light of the fact that the evidence for mutagenicity of cadmium is very limited. EPA's analysis has shown that a threshold model fits the data as well as a linear dose response model. The possibility of a threshold phenomenon should be evaluated with respect to the Thun data.

Thun has taken steps to estimate the potential effects of smoking and arsenic exposure on the worker population. However, the potential confounding effects of arsenic exposures in the workplace and the combined effects of smoking and arsenic cannot be ruled out as a potential cause of the increased cancer incidence at this time. It must be noted that the actual increase in cancer in the exposed group is fairly small. There were 7 cancers observed versus 4.6 cancers expected in the moderate exposure group. If it were found that these 7 workers with cancer had significantly higher arsenic exposure than the other members of this exposure category, the significance of this this study would have to be reevaluated. This type of nested case/control study is currently being performed by Dr. Thun. DHS should await the results of this study before finalizing their health effects evaluation.

Given the possible effects of arsenic exposure on the workers in the Thun study and the lack of a consistent dose response relationship in the epidemiological studies, EPA's conclusion of "limited evidence" of lung cancer risk from cadmium appears warranted. This lack of strong epidemiologic evidence, the possibility of nonlinear components in the dose response function, and potential confounding variables played a role in EPA's decision to recommend the maximum likelihood estimate of risk as the best single estimate. DHS should also refrain from recommending upper bound estimates of risk for purposes of extrapolation until the uncertainties in the occupational epidemiology studies can be resolved.

With respect to new data on cadmium and cancer, DHS should also consider obtaining the papers which will be presented at the Fifth International Cadmium Conference in San Francisco on February 4-6, 1986. Presentations by Dr. Thun and Dr. Lamm on February 6 may be of particular interest to DHS staff. Certainly the staff would want to incorporate any new information presented at this meeting before sending the report to the Scientific Review Panel for their review.

Edison appreciates being provided the opportunity to comment on this and other Toxic Air Contaminant documents. Again we apoligize for any inconvenience the minor delay in our submittal may have caused.

Sincerely,

Edward J. Tiedt

Cadmium Council, Inc.
292 Madison Avenue
New York, N.Y. 10017

212 578-4750

January 29, 1986

Mr. Richard Bode
California Air Resources Board
1800 15th Street
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Bode:

Enclosed are the Cadmium Council's comments on the Draft Report on Cadmium to the Scientific Review Panel.

Thank you for the opportunity of letting us comment on this document. If you have any questions, please contact me.

Sincerely,

Giovina L. Leone
Director, Environmental Health

cm
enclosure

BEFORE THE CALIFORNIA AIR RESOURCES BOARD

SACRAMENTO, CALIFORNIA

In the matter of: Draft Report to the Scientific Review Panel on Cadmium

COMMENTS OF THE CADMIUM COUNCIL, INC.

The Cadmium Council, Inc., is a non-profit trade association which represents producers, processors, and industrial users of cadmium in Canada and the United States. The Council's objective with regard to cadmium and health is to develop and disseminate information on the health effects of cadmium in order to assure the safe use of cadmium in the occupational and general environment. This is accomplished through the sponsorship of research on the potential health effects of cadmium exposure, publication of educational and training materials and dissemination of information including current developments in cadmium health research. This data base is subsequently used in the development of occupational and environmental regulations which assure the protection of health while being technologically and economically feasible.

Before continuing, I would like to thank the Air Resources Board on behalf of the members of the Cadmium Council for the opportunity to comment on the draft report on cadmium.

According to the draft, the Air Resources Board recommends that cadmium be listed as a toxic air contaminant because cadmium, stated unequivocally, is a human carcinogen. It is the purpose of these comments to provide the ARB with

information which will cast serious doubt on this statement. So much doubt that the EPA's final Updated Mutagenicity and Carcinogenicity Assessment Document could not provide solid evidence to support an unequivocal conclusion about cadmium's potential as a human carcinogen.

The EPA concluded that there was limited human evidence that cadmium causes lung cancer. The Council feels that even this conclusion is inaccurate in light of new evidence that would be contradictory. In addition, reanalysis of the key epidemiological study is still continuing. And, further work is also being done on confirmation of the key animal study. Until these studies are completed and conclusions are reached, the Cadmium Council feels that there is insufficient evidence that cadmium is a human lung carcinogen. Therefore, we feel that there is presently no scientifically sound basis for listing cadmium as a toxic air contaminant by the ARB.

The ARB's conclusion is a quantum leap from the EPA conclusion even though ARB has found no new studies to support such a definitive claim. In order to better understand why EPA reached a less definitive conclusion, it is important to have some background on the evolution of the EPA assessment document and its purpose.

The first draft of the health assessment document issued in 1983 reviewed the animal and epidemiological evidence concerning the carcinogenicity of cadmium and concluded that cadmium and certain compounds "probably" caused cancer of the prostate in humans. This was a radical departure from the 1981 version which concluded that there was no evidence sufficient to establish that cadmium might be a human carcinogen.

The EPA Cancer Assessment Group withdrew the 1983 draft because of comments which it received indicating significant negative evidence had not been considered which contradicted their conclusion that cadmium probably causes prostatic cancer.

Then in 1984, a second draft health assessment document was issued. After reconsidering their first conclusion, they decided that cadmium could only weakly be associated with prostatic cancer. But, they further concluded that new epidemiological evidence suggested that cadmium may cause lung cancer instead. This conclusion was based primarily on one chronic animal inhalation study by Takenaka and coworkers, but more importantly, on an epidemiological study by Dr. Thun of the National Institute of Occupational Safety and Health. Thun found an excess of lung cancer among workers employed for six months or longer at a U.S. cadmium production facility. The Cadmium Council's comments on this draft are provided as Appendix A.

The EPA Science Advisory Board's Metals Subcommittee met in October of 1984 at the University of Rochester to review the draft document. Among those giving public presentations were experts invited by the Cadmium Council. These experts included Dr. George Kazantzis of the U.K., Dr. Edja Hassler of Sweden, Dr. Steven Lamm from Washington, D.C., and Dr. Lowell White of ASARCO. Upon completion of the presentations, the Metals Subcommittee drafted recommendations for change to the documment (Appendix B). These recommendations were sent to the SAB Environmental Health Committee at which time they were considered along with written comments made by the public. The Cadmium Council submitted additional comments which summarized the presentations made before the Metals Subcommittee (Appendix C).

Even though the letter which was sent to the Administrator of EPA by the SAB agreed with the qualitative findings in the updated document, the SAB qualified their statement with several recommendations for further study.

The SAB was very critical of the quantitative risk assessment which was done by the Cancer Assessment Group recommending several changes and a reanalysis of the data.

Although the SAB found the Takenaka study to be sufficient evidence of cadmium's ability to cause cancer in animals, they felt more information was needed on the actual particle size distribution of ambient cadmium to which the general public would be exposed. This informtion would allow a comparison of the effective dose given to rats in the Takenaka study with typical human exposure for the purpose of quantitative risk assessment.

Of significance is the fact that the SAB recognized the effect of solubility on the bioavailability of various cadmium compounds and thus, a difference in their toxic potency. According to the ARB draft document, recent studies suggest absorption may not be dependant on solubility. The Oberdoerster et.al. (1979) study comparing the lung clearance of cadmium chloride versus cadmium oxide in rats was cited in support of this statement. However, the SAB subcommittee found that lesser solubility does effect the toxicity of some cadmium salts. For example, a rat inhalation study done by Rusch et.al. (1984, Fundam. Appl. Toxicol.) found cadmium red and yellow pigments to be much less bioavailable resulting in decreased absorption and toxicity when compared to cadmium carbonate and cadmium fume.

In addition, the SAB found Dr. Thun's analysis of the confounding effects of smoking to be reasonable and, therefore, not significant. However, Dr. Thun's analysis of arsenic as a confounding variable was criticized for not

using individual arsenic exposure levels. It was further recommended that the joint effect of cigarette smoking and arsenic exposure be examined.

The final document published in June of 1985, had no new evidence to support its conclusion that cadmium may cause lung cancer in humans. And, although the document did not reflect the public comments which criticized the animal and epidemiological studies upon which this conclusion is based, it did change its conclusion that there was sufficient evidence to regard cadmium as a mutagen. In addition, the quantitative risk assessment was recalculated according to SAB's recommendation.

Unfortunately, the SAB's additional recommendations were not included in the final document. It is interesting to note that in their letter to the EPA, they criticized the EPA Cancer Assessment Group for not including the recommendations they made on the previous draft. This is not to say that the SAB's comments fell on deaf ears. Indeed, Dr. Thun almost immediately went about collecting more data in an effort to resolve the confounding effects of arsenic exposure and smoking among his original cohort. Rather than stating this, the final document repeatedly argues that the Thun analysis adequately addressed these confounding variables despite the absence of new evidence.

Since the final document was published, Dr. George Kazantzis did a case control study for long cancer as part of a recently completed cohort mortality study of 6,995 male cadmium workers (Appendix D). This case control study was done in response to the finding of an excess risk of lung cancer in the low exposure group of this cohort. Dr. Kazantzis found that this excess risk of lung cancer was not due to cadmium, nor was the excess risk of bronchitis found in the medium exposure group.

In addition, the Fraunhofer Institute has begun a long-term inhalation study with cadmium which is a follow-up to the Takenaka study. In order to confirm its original findings, hamsters and mice will be exposed to four different cadmium compounds, including cadmium oxide. This study should be completed sometime in late 1986.

Another reanalysis of the ASARCO cohort is presently being conducted by Dr. Steven Lamm of CEOH in Washington, D.C.. Dr. Lamm's preliminary analysis shows that arsenic exposure and smoking could have caused the excess of lung cancer deaths seen in this cohort.

According to Dr. Lamm, plant history indicates three industrial eras with respect to arsenic at this work site. Prior to 1926, the arsenic plant on site was actively refining the arsenic trioxide, but crude arsenic was only stockpiled after 1940, when the feedstock arsenic content dropped to about 1%.

Analysis of cohorts by date of hire, rather than by dates of employment, is necessary to separate the effects from each exposure period. Little industrial hygiene data preceeds the 1950's. Analysis of the mortality data indicates a marked lung cancer risk for workers hired prior to 1926 (and working through 1940), a moderate excess lung cancer risk for workers hired between 1926 and 1940 (and working through 1940), and no excess lung cancer risk for those hired in 1940 or later. These data would suggest that arsenic exposure might be the major determinant of risk.

With regard to smoking, histories of smoking habits for workers from fifty years ago cannot be obtained. Adjustments of expected lung cancer risk for missing smoking information is generally based on assumptions of risk as a function of pack-years of exposures. But, pack-years of exposure assumes linerity in risk for both intensity of smoking and duration of smoking, while epidemiological analysis indicates that duration of smoking is a four order risk

factor. Methodology for adjusting expected risks for duration of smoking history need to be developed. Dr. Lamm has begun to assess the effects of arsenic exposure and smoking for this cohort. The results of this analysis will be presented at the International Cadmium Conference to be held in San Francisco, February 4-6, 1986.

In an effort to resolve these questions, the Cadmium Council is among the sponsors of the International Cadmium Conference and a workshop chaired by Sir Richard Doll specifically on cadmium and cancer. Sir Richard Doll, one of the most outstanding epidemiologists in the world, stated in a recent publication entitled "Occupational Cancer: Problems in Interpreting Human Evidence" that in his view, cadmium should not be regarded as a human carcinogen with reference to prostatic cancer (Appendix E).

According to Sir Doll:

> "It must be remembered too, that when an unexpected finding is observed and further studies are made to check it, the first set of data must be regarded as hypothesis-forming and excluded from the subsequent analysis. Failure to remember this led the members of a recent INTERNATIONAL WORKSHOP ON THE CARCINOGENICITY OF METALS (1981) into error when they concluded, on the advice of a committee which I chaired, that 'exposure to cadmium had contributed to the development of prostatic cancer' in four series of cadmium workers. The data that were available to the committee are summarized in Table 4, and these results were assessed as being likely to turn up by

Table 4 Prostatic Cancer in Cadmium Workers: Evidence Available in 1981

Country	Number Observed	Expected	Characteristic
Great Britain	4	0.6	Cases
U.S.A.	4	1.2	Deaths
Sweden (1)	2	1.2	Cases
Sweden (2)	4	2.7	Cases
All countries	14	5.6	

chance along only twice in a thousand had the first British series been omitted, as it should have been, a further 10 cases would have been counted against 5.1 expected, giving a one-tailed P value of 0.04, the conclusion that cadmium contributed to the causation of prostatic cancer would have been, at the most, tentative, and the results of the recent large-scale studies of all men occupationally exposed to cadmium in the whole of England, which are summarized in Table 5, would not have come as a surprise."

As evidenced by this example, errors in analysis of epidemiological data can be made easily when statistical evidence is evaluated improperly. However, an error in judgement is assured when statistical evidence is ignored completely. The following statement from the draft document implicating a cause and effect relationship between cadmium and prostatic cancer which totally disavows the statistical evidence must be deleted:

"Because the human studies repeatedly find some elevation in risk, albeit a non-significant one, the staff of DHS does not believe that there is evidence to reject an effect of cadmium on prostatic cancer."

This statement is nothing more than an editorial comment. Something that should be left out of a scientific document.

As far as cadmium's ability to cause lung cancer, Sir Doll concluded that very careful evaluation is required before a decision about such an effect is reached.

Health criteria aside, another reason for not listing cadmium is because airborne exposure to cadmium is minimal. This is according to an EPA Office of Water publication entitled "Cadmium Contamination of the Environment: An Assessment of Nationwide Risk". In particular, the report found that zinc and cadmium smelting is no longer a major source because of tighter controls of other emissions.

Based on this, and other information presented before an EPA public hearing on the notice to list cadmium under section 112, the EPA has decided to extend the comment period for 90 days in order for additional information to be compiled. A copy of the hearing transcript is provided as Appendix F.

In view of the uncertainties which exist with regard to cadmium's ability to cause lung cancer and studies that have found emissions of cadmium into the environment to be minimal, it would appear that the listing of cadmium as a toxic air contaminant is unwarranted. The Council recommends that this be considered by the ARB and that no further action be taken at this time.

Giovina L. Leone, M.S.
Director, Environmental Health

CIBA-GEIGY Corporation
Ardsley, New York 10502
Telephone 914 478 3131

CIBA-GEIGY

February 3, 1986

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
1102 Q Street
P. O. Box 2815
Sacramento, CA 95812

Attention: CADMIUM

Dear Mr. Loscutoff:

CIBA-GEIGY Corporation appreciates the opportunity to comment on the DRAFT REPORT TO THE SCIENTIFIC REVIEW PANEL ON CADMIUM. We regret that it could not be supplied by January 17 but it is our understanding that you will accept and consider our comments.

CIBA-GEIGY handles cadmium chemicals in the workplace and produces cadmium pigments for the marketplace. We are interested in the proper and appropriate regulation of cadmium and its compounds for the protection of workers and the general public. Your draft document represents an excellent review of the available data as well as an attempt to rationalize the classification of cadmium as a toxic air contaminant for the general population. This rationalization is based on animal and human data purported to prove that cadmium, per se, is a carcinogen and a statistical extrapolation of these data to a risk for the population of California.

Before this process is finalized we have some comments on the data reviewed and assumptions made that should be considered. In addition, certain new data are made available for your evaluation.

The Takenaka, et al cadmium chloride inhalation study showed what could be interpreted as a dose-response in lung tumor incidence. However, this continuous 18-month dosing insult did not produce a dose-related effect on time of tumor occurrence. It took 27 months for a significant tumor response to reveal itself. Cadmium chloride is known to increase both lung epithelial permeability and the number of inflammatory cells in the lung. These effects, taken together with the chemical's continual presence in the lung without any possibility for lung clearance and repair probably drastically affected the study results. The EPA draft document even states that "the potential of $CdCl_2$ for altering the normal phagocytic activity could explain why the investigators were able to produce such a marked carcinogenic response."

This brings us to the issue of threshhold with respect to the potential of cadmium posing an inhalation carcinogenic risk to the general population at ambient air concentrations. The DHS staff has concluded that non-carcinogenic toxicities exhibit a threshhold and ambient airborne cadmium will not pose a significant hazard. Both Takenaka, et al and the EPA allude to a relationship between lung cadmium retention, alteration of normal phagocytic activity, alveolar damage with enhanced cell proliferation and the carcinogenic activity of cadmium chloride. Table 1 gives the change in lung tumor incidence with respect to decreasing dosage.

TABLE 1

Dosage (ug Cd/m^3)	Total Lung Tumors	Percentage Change From Next Higher Dose
50	25	-
25	20	20
12.5	6	70
0	0	100

As can be seen there are disproportionate changes with successive dose halving. It thus appears likely that lower dosages cause less lung damage (considered a threshhold event) and consequently less lung tumors. This would indicate that ambient airborne cadmium does not pose a carcinogenic risk to the general population and should not be classified as a toxic air contaminant. The Takenaka, et al study also provides evidence supporting the DHS staff in concluding that ambient airborne cadmium will not cause renal toxicity since the highest exposure level only resulted in a concentration of 34 ug Cd/g wet weight of kidney.

Data developed by Thun, et al was used by DHS staff to calculate the human risk of lung cancer. This epidemiology study has been commented upon by numerous groups (Metals Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board, Cadmium Council and ASARCO). I have appended, rather than repeated, some of these comments. It is important to remember that this was an occupational, not ambient, exposure situation; levels were greater than 40 ug/m^3; working conditions varied over time with

decreasing cadmium exposures being evident; exposures to arsenic, lead and zinc also occurred; smoking habits could have accounted for half the increase; urine cadmium levels suggest a highly exposed population. Taken altogether this was a study that clearly demonstrated cadmium exposure (via urine) in a workforce that may not have consistently followed good hygiene practices and whose smoking habits were retroactively surmised. Workplace conditions which existed years ago can not be used to assess risk to the general population from ambient air exposure. It is of interest that Lauwerys, et al, (Toxicology Letters 23: 287-9, 1984) investigating the general populace living in industrial areas polluted by cadmium due to past emissions from non-ferrous metal industries found increased incidences of mortality related to nephritis and nephrosis but did not mention lung cancer even though the cause of death was obtained for each deceased person. This directly confirms the DHS staff position that renal effects are the most sensitive indicator and our position that extrapolation of lung cancer from worker exposure to the general population is not appropriate. Furthermore, no data from Japan suggests that non-occupational exposure to cadmium constitutes a carcinogenic hazard.

It is important to remember that all the inhalation epidemiology studies deal with exposures relating primarily and almost exclusively to battery production and ore smelting. These are hardly proper surrogates for the general population exposed to ambient air.

The lung is the most prevalent site of cancer in humans. Smoking is a recognized cause. The smoking histories in those studies purported to implicate cadmium as a lung carcinogen are either not available or are

sufficient to be considered a cause in themselves. Arsenic and nickel exposure also confound the issue. For instance, the EPA draft states the following about the Thun, et al study: "Of concern in this study is the possibility that the combined effect of increased cigarette smoking and exposure to arsenic might have served to produce the significant positive risk of lung cancer observed in this report. This possibility is all the more distinct because the risk of lung cancer in the study was not seen to be overwhelming. A subtle combination of factors such as the ones mentioned above could conceivably have served to produce the excess risks found, even though such an eventuality is unlikely. Thus, although this study cannot be said to be conclusive with respect to risks of lung cancer from exposure to cadmium, it constitutes the most clear-cut evidence yet leading to this conclusion." (Emphasis added.) Moreover, this statement appears to be at odds with a subsequent statement: "Strong evidence is available from the Thun et al. study that the significant two-fold excess risk of lung cancer seen in cadmium smelter workers is probably not due to the presence of arsenic in the plant or to increased smoking by such workers."

Any mathematically based risk assessment method dealing with a natural substance that ignores biological reality is flawed. In the case of cadmium, which is a substance that may be an essential trace element, biologic protective mechanisms (metallothionein production) exist to bind low levels and thus assist in preventing toxicity. To assume linear, no threshhold carcinogenic activity under these circumstances is biologically indefensible especially when a key inhalation study involves continuous

exposure over an eighteen month period under conditions which overwhelm the normal protective mechanisms in the lung. The body should be considered to have the capacity to repair any minimal DNA damage that might potentially occur from exposure of the general population to ambient levels of cadmium. The multistage model appears to assume that the likelihood of repair is not a dose-dependent process. The DHS staff alludes to these mechanisms though they end up stating that there is a finite probability that one molecule can cause a mutagenic or carcinogenic effect. Even if this were likely, some consideration should be given to how long it would take this one molecular hit to express itself as a cancer. If dose has any influence on the timing of this process and definitive cases take 20-40 years to be evident, then one molecule should induce a cancer long after the normal (or abnormal) life expectancy of an individual. The staff, in assuming no threshhold, states that there is always an excess cancer risk from exposure to any level of cadmium. By extension, this assumption would mean that any compound that has caused cancer in animals, without exception, will cause an excess cancer risk in people. This is not supported by the available evidence.

Another point worth covering is that all cadmium compounds are not alike with respect to toxicity or their absorption and distribution throughout the body. Table 2 compares the toxicity and absorption of various cadmium compounds. Note that cadmium sulfide, cadmium selenide, and cadmium sulphoselenide differ in acute toxicity from the other more soluble Cd compounds and that CdS has a slower lung absorption in the cat and dog. In addition, a study (Rusch, et al, submitted for publication and attached) was conducted comparing the acute toxicity, tissue distribution and rate of

elimination in rats following a 2-hour inhalation exposure to cadmium red, cadmium yellow, cadmium carbonate and cadmium fume. An equivalent dosage based on cadmium content was used for each test substance. There was no mortality in the control, cadmium red or cadmium yellow exposed groups. Mortality was 3/32 and 25/32 in the cadmium carbonate and cadmium fume exposed groups, respectively. Cadmium blood levels indicated that cadmium from the cadmium carbonate and fume was absorbed to a greater degree than cadmium from the red and yellow pigments. The majority of the elimination of cadmium following exposure to the two pigments was via the feces, with 80% being cleared within 24 hours. Elimination was slower following exposure to the carbonate and fume. The levels of cadmium in the liver and kidneys were many times higher following exposure to the carbonate and fume than following exposure to the red and yellow pigments. It is evident that cadmium compounds are not equivalent with respect to toxicity, absorption, distribution or excretion. Exposure to the two insoluble compounds, cadmium red and cadmium yellow did not produce mortality and resulted in more rapid elimination and far lower tissue levels of cadmium than was observed following exposure to the cadmium carbonate and cadmium fume.

A recent study by Oberdorster, et al (Toxicologist 5(1): 178, 1985) compared the toxicities of different Cd compounds to rat lungs. Cadmium sulfide had little if any effect on the measured parameters while $CdCl_2$ and CdO increased inflammatory cell influx and epithelial permeability.

Two other reports indicate the influence of solubility and physical state of cadmium compounds on toxicity and disposition. Aihara, et al

(Toxicology 36: 109-118, 1985) showed that a less soluble form of cadmium remained in the rat lung to a greater extent than a more soluble form with the latter increasingly being found over time in liver, kidney and intestine. Costa, et al (Cancer Research 42: 2757-2763, 1982) demonstrated that crystalline CdS was actively phagocytized by cells and induced morphologic transformation of Syrian hamster embryo cells while the amorphous form had significantly less activity at equivalent exposure concentrations and particle size.

The influence of metallothionein on cadmium has been investigated. Hart, et al (Toxicology 37: 171-179, 1985) exposed rats up to 30 times to a cadmium acetate aerosol via a nose only procedure at a concentration of 1.6 mg/m^3. Baseline cadmium lung levels rose 20-fold after 30 exposures while lung metallothionein increased 50-fold. Lee and Oberdorster (Toxicologist 5(1): 178, 1985) studied the fate of Cd-thionein in rat lung compared to cadmium chloride. They showed that $CdCl_2$ treated rats exhibited distinct clinical symptoms of general and lung toxicity which was not shown by Cd-thionein treated rats. Furthermore $CdCl_2$ was retained in the lung to a greater degree and was distributed to the liver while kidney was the primary organ with Cd-thionein. Takenaka, et al found relatively high lung cadmium levels considering that it was analyzed 13-months after the end of inhalation. This is especially true when comparing the Takenaka study to the work of Lee and Oberdorster, Rusch, et al, and Hart, et al. It is obvious that the Takenaka, et al study imposed a lung burden on the rats that bears no relationship to either larger amounts given for shorter periods or to ambient exposure of the general population.

In conclusion, we believe that the available animal and worker exposure data do not present a convincing picture that cadmium is a lung carcinogen presenting a risk to the general population of California through its presence in the ambient air. It should not be classified as a toxic air contaminant.

For your convenience, we are supplying copies of all references mentioned that are not on the literature list. In addition, the title page of a CEC document is included for completeness.

Very truly yours,

Martin E. Bernstein, Ph.D.
Manager, Toxicology

MEB:rp
Enclosure

COMPARATIVE EFFECTS OF CADMIUM COMPOUNDS

Premise: All Cadmium compounds are not equivalent with respect to toxicity and absorption.

CADMIUM COMPOUND	SPECIES	EFFECTS
CdS	Rat	Oral LD_{50} = >5 g/kg
CdSe	Rat	Oral LD_{50} = >5 g/kg
$CdCl_2$	Rat	Oral LD_{50} = 88-302 mg/kg
$Cd(Ac)_2$	Rat	Oral LD_{50} = 333 mg/kg
$CdCO_3$	Rat	Oral LD_{50} = 438-659 mg/kg
$Cd(NO_3)_2$	Rat	Oral LD_{50} = 397 mg/kg
CdO	Rat	Oral LD_{50} = 72-296 mg/kg
$CdSO_4$	Rat	Oral LD_{50} = 357 mg/kg
CdO, $CdCl_2$, CdS	Dog	CdO and $CdCl_2$ are more readily absorbed.
CdO, CdS	Cat	CdO - Immediate lung effects as well as liver and kidney activity. CdS - Delayed effects (24-36 hrs.) limited to lung. Attributed to mechanica effect of blocking passageways due to insolubility and slow absorption.
CdO	Mice	Acute Oral LD_{50} = 72 mg/kg
$CdSO_4$	Mice	Acute Oral LD_{50} = 88 mg/kg
$CdCl_2$	Mice	Acute Oral LD_{50} = 93.7 mg/kg
$Cd(NO_3)_2$	Mice	Acute Oral LD_{50} = 100 mg/kg
CdS	Mice	Acute Oral LD_{50} = 1166 mg/kg
CdS-CdSe	Mice	Acute Oral LD_{50} = 2425 mg/kg

CalMat Co

9300 FLAIR DRIVE/P O BOX 5210/EL MONTE, CALIFORNIA 91734-1210/(818) 307-8933

February 12, 1986

Mr. Richard Bode
ARB/Scientific Review Panel
1800 15th Street
P.O.Box 2815
Sacramento, CA 95812

Re: Report to the Scientific Review Panel on Cadmium

Dear Mr. Bode:

On behalf of our California Portland Cement Company subsidiary, I wish to comment upon the estimated cadmium emissions from portland cement manufacturing in California, as set forth in the January 1986 "Report to the Scientific Review Panel on Cadmium". I unfortunately did not receive this Report until February 6; after the February 5 deadline for submitting public comments. However, because the Cd emissions estimate in the Report appears to be overestimated by at least two orders of magnitude, I submit the following in the anticipation that corrections can be made prior to the ARB hearing on listing Cd as a toxic air contaminant.

On Table III, "Overview and Recommendation" (p.7), and Table II-1 "Sources of Atmospheric Cadmium" (p.II-5), the 1981 estimated emissions of Cd from cement manufacturing are listed as 6.5 tons/year. Calculations of this emission rate are presented in Appendix C (page C-4). An analysis of these calculations follows:

1. California Cement Production in 1981

The report states that 2.93×10^7 tons of cement were produced in 1981. This is incorrect and overstates the production by a factor of 3.7. Attached is the U. S. Bureau of Mines "Mineral Industry Survey, Cement Annual Advance Summary", July 15, 1982. Table 2 (p.4) lists the 1981 combined Northern and Southern California cement production as 7,878,000 tons.

For the purposes of estimating emissions, however, clinker production is relevant. Portland cement clinker is the intermediate material produced in the rotary kiln - the equipment from which the emissions in question emanate. Portland cement is manu-

factured by intergrinding the clinker with approximately 5% gypsum. Table 3 (p.5) of the USBM report lists the 1981 combined Northern and Southern California clinker production as 7,719,000 tons.

2. Tons of Feed Material

Approximately 1.6 tons of feed material to the rotary kiln is needed to produce one ton of clinker (not cement, as stated in the report). Thus, the total tons of kiln feed used in 1981 to produce clinker, by both wet and dry process kilns, was

$$1.6^{*}\ 7.72 \times 10^{6} = 12.4 \times 10^{6} \text{ tons kiln feed}$$

3. Total Kiln Particulate Emissions

All rotary kilns in California, wet or dry, are equipped with fabric filter baghouses or electrostatic precipitators to remove particulates from the kiln exhaust gases. Although I cannot provide appropriate documentation, it is conservative to assume, on a statewide average basis, that total particulate emissions from these control devices comply with the U.S.EPA Standards of Performance for New Stationary Sources, Subpart F, Portland Cement Plants. The relevant standard for rotary kilns (40CFR 60.62(a)(1)) limits total particulate emissions to 0.3 lb per ton of kiln feed. Thus, total 1981 particulate emissions from rotary kilns in California are estimated to be:

$$12.4 \times 10^{6} \text{ tons kiln feed} \ \frac{*\ 0.3 \text{ lb particulate}}{\text{ton kiln feed}} = 3.71 \times 10^{6} \text{ particulat}$$

4. Total kiln Cadmium Emissions

Similar to the methodology used by the CARB/DHS staffs for the Chromium toxic emissions report, it is appropriate to assume that the concentration of Cadmium in the rotary kiln baghouse/ESP particulate emissions is equal to the Cd concentration in the dust removed by these control devices (there are no data, of which I am aware, on the Cd concentration in the directly emitted particulate). Attached is a copy of the US Bureau of Mines report "Charterization of U.S. Cement Kiln Dust" (IC8885, 1982) by Haynes and Kramer. As part of this study, 113 samples of kiln dust from 102 U.S. plants (11 in California) were analyzed for trace element concentrations.

The trace element concentrations in the 113 individual kiln dust samples are listed in Table 7 (pp.13-15). As the eleven samples from California cement plants are not separately identified, the the concentration summary in Table 8 (p.16) must be used. For Cadmium, the mean concentration is 21 μg/g, or 21 ppm by weight.

Using this Cd concentration and the total kiln particulate emissions, the 1981 Cd emissions from cement manufacturing are estimated to be:

$$\frac{21 \text{ parts Cd}}{10^6 \text{ parts particulates}} * \frac{3.71 \times 10^6 \text{ lb particulate}}{\text{year}} * \frac{\text{ton}}{2000 \text{ lb}}$$

$$= \underline{\underline{0.039 \text{ ton Cd/yr}}}$$

Please let me know if you or the relevant staff representatives have any questions regarding these calculations. As part of the California cement manufacturing industry, we feel that it is most important that the toxic air contaminant report for Cadmium, as well as the forthcoming trace elements, reflect the best stationary source emissions estimates.

Sincerely,

Dr. David S. Cahn
Vice President-Regulatory Matters

Attachments

cc: P. Hawkins

IC 8885

Bureau of Mines Information Circular/1982

Characterization of U.S. Cement Kiln Dust

By Benjamin W. Haynes and Gary W. Kramer

UNITED STATES DEPARTMENT OF THE INTERIOR

MINERAL INDUSTRY SURVEYS

U. S. DEPARTMENT OF THE INTERIOR
BUREAU OF MINES
WASHINGTON, D.C. 20241

James G. Watt, Secretary — Robert C. Horton, Director

For information call Sandra T. Absalom,
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Riena M. Lacroix, statistical assistant,
Telephone: (202) 634-1184

CEMENT IN 1981

U.S. cement consumption and production slumped in 1981 to the lowest levels since 1975, according to the Bureau of Mines, U.S. Department of the Interior. Cement demand, which declined for the second successive year, reflected reduced activity in the construction industry and general weakness in the U.S. economy. For example, total value of construction, in terms of constant (1977) dollars, decreased 3.5% to $155 billion, according to data published by the U.S. Department of Commerce. Housing starts decreased 16% to 1.1 million units.

Imports, a sensitive indicator of domestic cement demand, declined 24% to 4 million tons, and accounted for 5% of consumption, compared with 7% in 1980. Clinker imports were 31% of the total, compared with 36% in 1980. In a display of optimism for recovery in cement demand, several terminals for transshipment of imported cement began operations in California, Maine, and New York.

Shipments of portland and masonry cement from U.S. plants, excluding Puerto Rico, at 71.7 million tons, were 6% less than 1980 shipments and 16% less than 1979 shipments. No regional shortages occurred during 1981. Shipments decreased by at least 5% to all geographical regions except New England (up 1%), and the West South Central and Mountain regions (up 2% each). Shipments declined most severely to the East North Central (down 13%) and Pacific regions (down 12%).

Two new plants in Alabama and Utah collectively added more than 2 million tons per year to domestic cement production capacity in 1981. Seven other plants completed modernization programs that added approximately 3.5 million tons to U.S capacity. Most of these plant expansions occurred in California, and all of them were west of the Mississippi River.

Prepared in the Division of Industrial Minerals, July 15, 1982.

CIBA-GEIGY Corporation
Ardsley, New York 10502-2699
Telephone 914 478 3131

CIBA-GEIGY

June 18, 1986

Mr. Cliff Popejoy
California Air Resources Board
1102 Q Street
P. O. Box 2815
Sacramento, California 95812

Re: Cadmium

Dear Mr. Popejoy:

Enclosed, as discussed, is a toxicology report on studies in progress on various cadmium compounds. These long term rodent inhalation experiments show that different cadmium compounds exhibit dissimilar toxicity and distribution patterns, a conclusion that can be demonstrated by comparing the groups with similar exposure schedules.

Thus, hamsters exposed to cadmium oxide for 49 weeks at a concentration of 90 ug/m^3 showed a similar mortality to those exposed to cadmium sulfide pigment for 44 weeks at 1000 ug/m^3, a dose which was approximately 10 times greater.

Additionally, the distribution patterns in these two groups also showed differences between cadmium oxide and cadmium sulfide. Analysis of lung concentrations revealed that the cadmium sulfide exposed animals had about 15 times more cadmium present than the cadmium oxide exposed animals but similar kidney levels. This could indicate that increased lung levels of insoluble cadmium sulfide pigment are excreted via the gastro-intestinal tract rather than being absorbed into the circulation and distributed to the kidneys.

Furthermore, the cadmium sulfide exposed hamsters did not have lung edema or proteinosis which was seen in hamsters and mice exposed to lower concentrations of cadmium oxide for shorter periods of time. In addition, the cadmium sulfide hamsters had a lower incidence of bronchio-alveolar hyperplasia, lung cholesterol crystal deposits and fibrosis when the differences in concentration and exposure time are taken into account.

According to Dr. Heinrich, no cadmium-related carcinogenic effects have been observed in any of these experiments as of March, 1986. I will keep you informed of any additional information on these studies.

Yours truly,

Martin E. Bernstein, Ph.D
Manager, Toxicology
Safety, Health & Ecology

pop686/gm
Enc.

Inhalation Experiments in Rodents for Testing the Carcinogenicity of Cadmium Compounds

U. Heinrich, R. Fuhst, H. König, L. Peters, F. Pott, S. Takenaka
Fraunhofer Institut für Toxikologie und Aerosolforschung
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Society of Toxicology, 25th Anniversary Meeting, March 3-7,
1986, New Orleans, Louisiana
Poster Session

Inhalation of 12.5, 25 and 50µg Cadmium/m³ in $CdCl_2$ for about 150 hrs/week for 18 months induced lung carcinomas in rats (Takenaka et al. 1983). Therefore the carcinogenic effect of other Cadmium compounds and the susceptibility of other species should be investigated.

In this ongoing experiment male and female Syrian golden hamsters and female mice (NMRI) are exposed to aerosols of 4 different Cadmium compounds on 5 days/week, for 19 hrs/day or 8 hrs/day for 12-18 months. After termination of the exposure the animals are kept in clean air for another 6-12 months. The Cd-exposure is terminated prematurely if there is a substantial loss of body weight or increased mortality.

The Cd-aerosols are generated by atomizing $CdCl_2$ and $CdSO_4$ solutions and by nebulizing CdS suspensions. CdO dust aerosols are produced by atomizing Cd-acetate solutions with subsequent pyrolization of the Cd-aerosol at 750°C. The CdO fumes are generated by evaporation and oxidation of metallic Cd from Cd electrodes in an electric arc.

The particle size (mass) distribution is measured by a 8-stage cascade impactor. The mass median aerodynamic diameter of the aerosols is 0.2 - 0.6um.

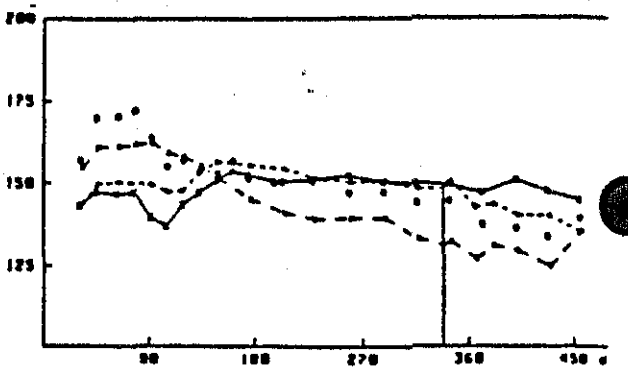
The Cd-concentration in the horizontal flow exposure chambers is determined daily by analyzing filter samples.

At the end of the experiment a comprehensive histopathological examination will be performed and the Cd content of lung, liver and kidney will be determined.
Some preliminary results are reported.

Experimental Plan

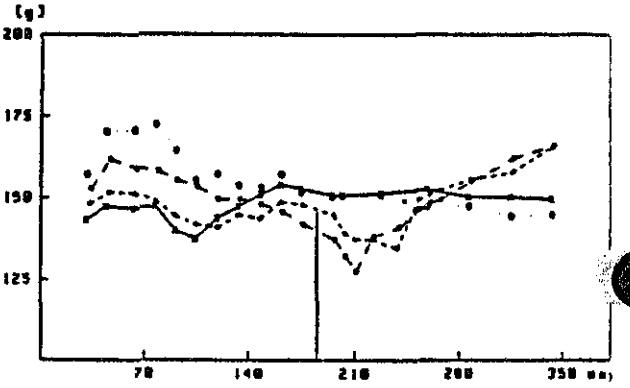
Substance-Concentration (µg Cd/m³)	Exposure Time (hrs/d•y)	Exposure Time (weeks) hamsters/mice	Experimental Time (weeks) hamsters ♂ / ♀ / mice ♀
clean air	-	- / -	• / 85 / •
clean air	-	- / -	• / 76 / •
clean air	-	- / -	• / • / •
clean air	-	- / -	• / • / •
$CdCl_2$-30	19	• / •	• / • / •
$CdCl_2$-90	19	59 / 42	• / 76 / 81
$CdSO_4$-30	19	• / •	• / • / •
$CdSO_4$-90	19	60 / 42	• / 81 / •
CdS-90	19	• / •	• / • / •
CdS-270	8	26 / 26	• / • / •
CdS-270	19	60 / 59	70 / 64 / •
CdS-1000	19	44 / 41	59 / 60 / 70
CdO-10	19	• / •	• / • / •
CdO-30	19	59 / 59	• / 85 / •
CdO-90	8	• / •	• / • / •
CdO-90	19	52 / 52	73 / 68 / 33
CdO-270	8	• / •	• / • / •
CdO-270	19	26 / 11	51 / 51 / 81
CdO-fume-10	19	58 / 58	• / 79 / •
CdO-fume-30	19	52 / 52	• / • / •
CdO-fume-90	8	• / •	• / • / •

n = 24 hamsters ♂, 24 hamsters ♀, 48 mice ♀
• = still in progress



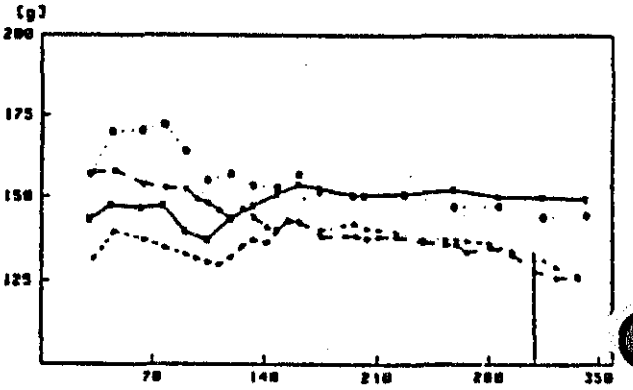
Body weight of the hamsters exposed to

—•— Gr.-No. 1 (♂♂) Clean air
·0· Gr.-No. 2 (♀♀) Clean air
---•--- Gr.-No. 7 (♂♂) CdO (90 µg Cd/m³)
— -•- — Gr.-No. 8 (♀♀) CdO (90 µg Cd/m³)



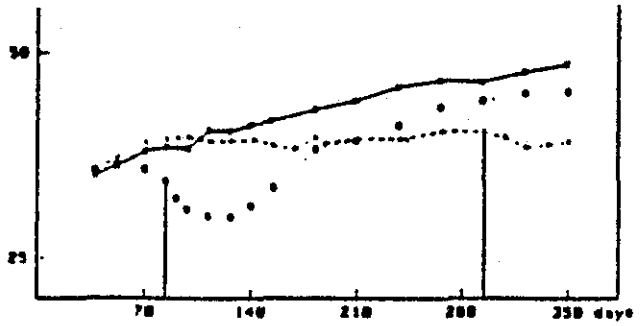
Body weight of the hamsters exposed to

—•— Gr.-No. 1 (♂♂) Clean air
·0· Gr.-No. 2 (♀♀) Clean air
---•--- Gr.-No. 11 (♂♂) CdO (270 µg Cd/m³)
— -•- — Gr.-No. 12 (♀♀) CdO (270 µg Cd/m³)



Body weight of the hamsters exposed to

—•— Gr.-No. 1 (♂♂) Clean air
·0· Gr.-No. 2 (♀♀) Clean air
- -•- - Gr.-No. 17 (♂♂) CdS (1000 µg Cd/m³)
·-•-· Gr.-No. 18 (♀♀) CdS (1000 µg Cd/m³)



Body weight of the mice exposed to

—•— Gr.-No. 18 (♀♀) Clean air

0 Gr.-No. 23 (♀♀) CdO (270 µg Cd/m³)

------ Gr.-No. 27 (♀♀) CdS (1000 µg Cd/m³)

Body Weight Development

------- End of Exposure

Cadmium Content of Mouse Lung, Liver and Kidney at the End of the Experimental Time (Exposure + Clean Air Time)

Exposure Concentration	Exposure Time (Weeks)	Clean Air Time (Weeks)	µgCd/g wet Weight		
			Lung	Liver	Kidney
CdO 270µgCd/m³	11	51	15.5 ± 7.9	7.2 ± 3.4	66.3 ± 19.9
CdS 1000µgCd/m³	41	29 - 30	338 ± 130	29.1 ± 8.8	189 ± 26

Mortality Rate after Termination of Cd Exposure

Exposure Concentration	Exposure Time (Weeks)	Mortality		
		Exposed	Controls	
CdO 90 µgCd/m³	49 (♂)	12 %	0 %	Hamsters
	49 (♀)	21 %	8 %	
CdO 270 µgCd/m³	26 (♂)	8 %	0 %	
	26 (♀)	4 %	0 %	
CdS 270 µgCd/m³	60 (♂)	25 %	8 %	
	60 (♀)	79 %	29 %	
CdS 1000 µgCd/m³	44 (♂)	17 %	0 %	
	44 (♀)	21 %	8 %	
CdS 1000 µgCd/m³	41 (♀)	38 %	6 %	Mice
CdO 270 µgCd/m³	11 (♀)	0 %	0 %	

Even the exposure of hamsters to only 90ug Cd/m³ in CdO for 19 hrs/day caused an increased mortality after an exposure time of less than 1 year.

Cadmium Content of Hamster Lung, Liver and Kidney at the End of Experimental Time (Exposure + Clean Air Time)

Exposure Concentration	Exposure Time (weeks)	Clean Air Time (weeks)	µg Cd/g Wet Weight		
			Lung	Liver	Kidney
CdO 90 µgCd/m³	49	15 (♂)	38.5 ± 4.5	31.8 ± 8.4	26.3 ±
		40 (♂)	18.7 ± 3.5	26.1 ± 9.1	48.5 ±
		16 (♀)	31.5 ± 5.9	10.6 ± 2.5	44.5 ±
CdO 270µgCd/m³	26	25 (♂)	27.7 ± 6.8	22.1 ± 5.9	72.9 ±
		25 (♀)	28.8 ± 3.2	14.7 ± 4.1	60.4 ±
CdS 270µgCd/m³	60	7-10 (♂)	217 ± 38	19.1 ± 3.5	70.5 ±
		2-4 (♀)	214 ± 21	14.7 ± 1.9	61.9 ±
CdS 1000µgCd/m³	44	11-15 (♂)	542 ± 126	50.7 ± 20.8	28.4 ±
		14-17 (♀)	540 ± 77	30.5 ± 7.5	55.7 ±

Due to very low solubility of CdS, there was no major difference in the kidney Cd-content of hamsters exposed to 90ug Cd in CdO or 1000ug Cd in CdS (Tab.7).

Compared to the CdO group the content of the lungs of the CdS exposed animals at the end of the experiment was about 15 times higher (Tab.8).

Even 51 weeks after termination of the exposure to 270ug Cd in CdO (11weeks), the Cd-content in the mouse lung was still 16ug/g w.wt. (Tab.9).

The Cd-content of the various organs of control animals was far below 1ug/g w.wt.

The Cd-concentration was determined on a Perkin-Elmer 2380 atomic absorption spectrophotometer equipped with an air-acetylene burner. The tissue samples (0.25g) were digested with nitric acid under pressure at 160°C.

Cadmium Content of Hamster Kidney 1 - 4 Weeks after Termination of Exposure

Exposure Concentration	Exposure Time (Weeks)	µgCd/g Wet Weight	
		♂	♀
CdO, 90µgCd/m³	49	54.4 ± 21.6	26.7 ± 10.7
CdO, 270µgCd/m³	26	78.4 ± 19.8	85.7 ± 24.5
CdS, 270µgCd/m³	60	77.1 ± 10.9	43.2 ± 24.3
CdS, 1000µgCd/m³	44	74.4 ± 30.2	24.9 ± 15.5

Preliminary Histopathological Findings

a) Mice, 270ug Cd/m³ in CdO, 11 Weeks of Exposure + 51 Weeks Clean Air.

Lung:	Incidence
histiocytosis (foamy macrophages)	71 %
oedema/proteinosis	39 %
cholesterol crystals	50 %
thickened septa (fibrosis)	61 %

Kidneys, Liver: no exposure related changes.

b) Hamsters, 270ug Cd/m³ in CdO, 26 Weeks of Exposure + 25 Weeks Clean Air.

Lung:	Incidence ♂	♀
histiocytosis (foamy macrophages)	100 %	94 %
bronchio-alveolar hyperplasia	73 %	83 %
oedema/proteinosis	63 %	34 %
cholesterol crystals	50 %	52 %
thickened septa (fibrosis)	43 %	28 %
Kidneys:		
nephrosis/amyloidnephrosis (probably not Cd induced)	60 %	60 %

Liver: no exposure related changes.

c) Hamsters, 1000ug Cd/m³ in CdS, 44 Weeks of Exposure + 14 Weeks Clean Air.

Lung:	Incidence ♂	♀
histiocytosis (foamy macrophages)	100 %	100 %
bronchio-alveolar hyperplasia	43 %	65 %
oedema/proteinosis	0 %	0 %
cholesterol crystals	19 %	30 %
thickened septa (fibrosis)	24 %	48 %
Kidneys:		
nephrosis/amyloidnephrosis (probably not Cd induced)	76 %	78 %

Liver: no exposure related changes.

Conclusions:

1) No bronchio-alveolar hyperplasia is found after 11 weeks of CdO exposure in mice but after 26 weeks of exposure in hamsters.

2) Oedema/proteinosis were not observed in CdS exposed hamsters.

California Council for Environmental and Economic Balance

1512 - 14th Street Sacramento, CA 95814 • (916) 443-8252

August 20, 1986

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

RE: Cadmium

Dear Mr. Loscutoff:

The Council has reviewed the revised draft health effects report on cadmium, and appreciates the opportunity to submit these brief comments on several important policy matters that are addressed in the report. We are concerned that the health effects assessment does not accurately reflect the range of risk that may be posed by cadmium, because Department of Health Services' staff has chosen to exclude the very real possibility that there may indeed be no risk at measured ambient concentrations.

We can understand the basis for incorporation of the worst case policy assumptions DHS uses to emphasize the maximum possible upper bound risk (although we believe that risk assessments should also present the "most likely" risk estimate). However, such emphasis should not exclude an objective presentation of the very real possibility that a threshold may exist at concentrations a thousand times higher than the highest average concentration reported in California. In its 1985 "Updated Mutagenicity and Carcinogenicty Assessment of Cadmium", EPA objectively presented the possibility that a threshold might exist, and indicated that under such a thresholod assumption, a constant lifetime exposure to 10 micrograms per cubic meter would produce zero risk.

While we recognize that the existence of a threshold cannot be proven or disproven, the Air Resources Board needs to know the relative weight of the evidence regarding the plausibility of such thresholds when it is faced with making risk management decisions. The report does not convey to decision makers the particularly high degree of uncertainty associated with the estimated risk for such low levels as

those measured in the state. Accordingly the Council recommends tha the health effects assessment be revised to state that the risk is estimated to be zero to 12 cases per million persons exposed to 1 ng/m^3. We also recommend that all future risk assessments contain a similar objective presentation of the threshold model.

Sincerely,

Evelyn F. Heidelberg

Evelyn F. Heidelberg
Vice President

EFH:cpr

CIBA-GEIGY Corporation
Ardsley, New York 10502-2699
Telephone 914 478 3131

CIBA–GEIGY

August 18, 1986

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

RE: CADMIUM

Dear Mr. Loscutoff:

CIBA-GEIGY Corporation appreciates the opportunity to comment on the June, 1986 revisions to Part B of the ARB Report on Cadmium.

Your group has continued its rational approach for dealing with a difficult issue, namely, whether substances present in the ambient air present a risk for the population of California. Your conclusion that cadmium is a toxic air contaminant is based on a risk assessment made by extrapolating data from the Thun, et al. study which purportedly demonstrates a relationship between occupational cadmium exposure and an increased incidence of lung cancer. A number of assumptions and conclusions have been made in the assessment process that require comment.

1. Thun, et al. (1985).

This study forms the basis of your assessment. It is currently undergoing a more detailed review. This will be discussed at an upcoming symposium, chaired by Sir Richard Doll, dealing specifically with the adequacy of epidemiologic studies on cadmium to classify it as a carcinogen. We have learned that at least one person whose lung cancer was attributed to cadmium is also included in another study where his lung cancer has been attributed to asbestos. In addition, a previously unconsidered confounding variable is possible exposure to radon. The plant under investigation is located in Colorado. To my knowledge no radon measurements have ever been made either at the plant site or in the surrounding communities. Since radon can cause lung cancer, this is an important factor which should be clarified.

2. Threshold/Non-Threshold Concept.

This matter was discussed in our previous comments. It is of interest that your reviewers consider negative in vivo mutation studies as being insensitive tests as opposed to being indicative that the body can effectively handle small doses of cadmium; i.e., exhibit threshold characteristics, at concentrations that might be present in ambient air. In fact, the absence of a carcinogenic effect in the Thun study at the two lowest doses indicates that a threshold does exist even in the workplace and would exist for ambient air where exposure is a thousandfold less. According to the authors, "The excess of deaths from lung cancer was statistically significant only for the stratum of workers whose cumulative exposure to cadmium exceeded 2920 mg-days/m^3, the level corresponding to a 40-year exposure above the current OSHA limit (200 ug/m^3). Workers whose cumulative exposure was below the 40-year equivalent of the NIOSH recommended TWA of 40 ug/m^3 showed no excess of lung cancer deaths."

Support for the concept of a threshold is derived from two other facts. First of all, excess cadmium can stimulate metallothionein synthesis which is known to detoxify cadmium following continuous low level exposure (Webb, M. (1979) in "Metallothionein", Kagi & Nordberg, editors, pp 313-20). Secondly, it is known that zinc and cadmium interact and compete for protein and enzyme binding sites. Your own reviewers acknowledge that zinc can reverse and/or prevent cadmium toxicity. The Thun study demonstrated that a critical concentration of cadmium was achieved only with the high dose workers. This critical concentration or threshold was not reached with the low dose workers. It would similarly not be reached by the general population of California which is exposed to relatively low ambient air levels of cadmium and which has zinc available in food, ambient air and mineral supplements.

3. Other Considerations.

3.1 Ambient Air - Occupational Exposure Relationships.

The use of occupational health standards to obtain an ambient air level is controversial and not uniformly accepted. Calabrese (Regulatory Toxicology and Pharmacology 6: 55 - 9, 1986) has stated, however, that "the methodology of dividing the TLV by 420 is consistently more conservative or protective than that derived from actual data". The ACGIH TLV for cadmium is 50 ug/m^3; dividing by 420 gives a safe ambient air level of 120 ng/m^3. Adoption of this value would provide a 3-fold safety factor over the "hot spots" and an approximate 50-fold safety factor over average California ambient air.

3.2 Dose Rate - Total Dose

At least one carcinogenicity study compared the relative effects of dose rate versus total dose (Littlefield, N. A. and D. W. Gaylor, J. Toxicol. Envir. Health 15: 545 - 50, 1985). In this study, it was found that "when the total doses were similar, the higher dose rates for shorter time periods induced a higher prevalence of tumors. Those groups dosed at higher rates but for fewer months had a generally higher prevalence than those receiving similar total doses but at lower rates for more months".

Certain cadmium inhalation studies in the rat also show the influence of dose rate. Oldiges & Glaser (Trace Elements in Medicine 3: 72-5, 1986) administered cadmium oxide continuously to Wistar rats for 22 hours/day, 7 days a week for either 218 or 324 days at a concentration of 90 ug/m^3. Exposure had to be terminated at this point because 12/40 animals had died. In the context of the interaction between zinc and cadmium discussed earlier, it is of interest that this concentration of cadmium oxide did not cause any mortality in 40 rats exposed simultaneously to zinc oxide for 374 days. In contrast, in a study by Kaplan, Blackstone & Richdale (ERDA Symp. Ser. 42, 77-97, 1977), Sprague-Dawley rats tolerated exposure to cadmium oxide at a concentration of about 300 ug/m^3 for 7-8 hours/day, 5 days/week for 9-13 months without any reported mortalities.

3.3 Effect of Smoking

It is acknowledged that cigarette smoking can contribute to the body load of cadmium. Post, Johansson & Allenmark (Environ. Res. 34: 29-37, 1984) autopsied 5 male heavy smokers between 65 and 78 years of age within about 3 days postmortem. They measured cadmium levels and degree of protein binding in the lungs, liver and kidneys. They found that human lungs contain a low molecular weight protein which binds cadmium and which appears to be similar to that found in the liver and kidneys. A lesser degree of cadmium binding was seen in the lungs compared to liver and kidneys.

3.4 Extrapolation

The extrapolation of animal studies to estimate human risk requires sophisticated statistical procedures and many conservative biological assumptions. Therefore, the use of human data is always preferred in estimating human risk. Thus, it is of interest that methods for species extrapolation were used with the data from the Thun, et al. human epidemiology study, which demonstrated a purported effect group (high-dose), a no-effect group (low-dose), and an intermediate effect group (mid-dose). Extrapolation should not be necessary for an adequate human study which demonstrates a no-effect level, particularly at a dose many times higher than ambient air concentrations.

In summary, we have presented our rationale for not considering cadmium as a toxic pollutant at ambient concentrations. Our reasoning is based on the facts that data exist showing that human lung tissue contains a cadmium binding protein considered to be metallothionein. Metallothionein is known to detoxify cadmium at continuous low levels of exposure. Zinc can also reverse and/or prevent cadmium toxicity. Animal studies have clearly demonstrated that different responses to inhaled cadmium exist and are related to a concentration-time response. Human epidemiology studies have shown that a toxic dose rate is many orders of magnitude higher than what the general population of California could experience at ambient air levels of cadmium. We contend, therefore, that no basis exists for classifying cadmium as a toxic air contaminant at ambient air concentrations nor is there substantiation for being "unable to identify a level below which adverse health effects are not expected to occur."

I have enclosed one copy of each article mentioned.

Yours truly,

Martin E. Bernstein/dck

Martin E. Bernstein, Ph.D
Manager, Toxicology

MEB7/21/vk
Encs.

Mortality Among a Cohort of U.S. Cadmium Production Workers—an Update [1]

[redacted]beal J. Thun, *M.D., M.S.*,[2] Teresa M. Schnorr, *Ph.D.*,[2] Alexander Blair Smith, *M.D., M.S.*,[2] [redacted]am E. Halperin, *M.D., M.P.H.*,[2] *and* Richard A. Lemen, *M.S.*[2,3]

ABSTRACT—A previous retrospective mortality study of 292 U.S. cadmium production workers employed for a minimum of 2 years showed increased mortality from respiratory and prostate cancer and from nonmalignant lung disease. To examine further the mortality experience of these workers, investigators from the National Institute for Occupational Safety and Health extended the study to include 602 white males with at least 6 months of production work in the same plant between 1940 and 1969. Vital status was determined through 1978, which included the addition of 5 years to the original follow-up. Cause-specific mortality rates for seven causes of death potentially related to cadmium exposure were compared between the overall cohort and U.S. white males and between subgroups. Mortality from respiratory cancer and from nonmalignant gastrointestinal disease was significantly greater among the cadmium workers than would have been expected from U.S. rates. All deaths from lung cancer occurred among workers employed for 2 or more years. A statistically significant dose-response relationship was observed between lung cancer mortality and cumulative exposure to cadmium. A 50% increase in lung cancer mortality, which was not statistically significant, was observed even among workers whose cumulative exposure to cadmium was between 41 and 200 $\mu g/m^3$ over 40 years. Since the previous investigation, no new deaths from prostate cancer and no excess of deaths from nonmalignant respiratory disease have been observed.—JNCI 1985; 74:325-333.

In 1976, Lemen et al. (*1*) published the results of a study on cancer mortality among cadmium production workers at a U.S. cadmium recovery plant. Using national white male rates for comparison, Lemen et al. reported a statistically significant excess of deaths from respiratory cancer (Obs=12; SMR=235), from nonmalignant respiratory disease (Obs=8; SMR=159), and, among workers with 20 or more years since first employment, from prostate cancer (Obs=4; SMR=452). The Lemen study included only hourly workers employed for 2 or more years between January 1, 1940, and December 31, 1969, and followed these workers through 1973.

A number of previous epidemiologic and experimental studies had suggested that cadmium might cause cancer of the prostate. Two occupational reports (*2, 3*) described excess mortality from prostate cancer among cadmium workers at a small British alkaline battery plant. Cadmium, like zinc, is known to concentrate in the prostate gland (*4-5*). Numerous toxicologic studies (*6-13*) have shown that injection of cadmium metal or salts into laboratory rats produces sarcomas locally and more distant interstitial cell tumors of the testes. On the basis of these findings, the IARC (*14*) concluded in 1976 that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man." Substantial controversy continues, however, and although several subsequent epidemiologic studies (*15-18*) have found increased mortality from prostate cancer among occupational groups, other studies (*19-21*) have not.

Still more controversial is the possible relationship between cadmium and lung cancer. At the time of the IARC working committee, only the Lemen et al. (*1*) study had found excess mortality from respiratory cancer. Interpretation of that study was complicated because some of the long-term workers in the cohort also had been exposed to arsenic during the 1920's when the plant functioned as an arsenic smelter. Concern about the potential carcinogenicity of cadmium to the lung has increased, however, due to recent animal data. Takenaka et al. (*22*) exposed rats continuously to cadmium chloride aerosol and found a dose-dependent increase in lung tumors at exposure levels well within the current occupational limit.

Because of continuing concern about the effects of chronic cadmium exposure on mortality, NIOSH has extended the follow-up of the cohort first described by Lemen et al. (*1*). The present report describes the mortality experience of the group through 5 additional years of observation, ending December 31, 1978. In

Abbreviations used: CI=confidence interval; Exp=expected; HIS=Health Interview Survey; IARC=International Agency for Research on Cancer; ICD=International Classification of Disease; NIOSH=National Institute for Occupational Safety and Health; NMGID=nonmalignant gastrointestinal disease; Obs=observed; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; PY=person-years; PYAR=PY at risk of dying; SMR=standardized mortality ratio(s); SRR=standardized rate ratio(s); TWA=time-weighted average.

[1] Received April 16, 1984; accepted August 20, 1984.

[2] Robert A. Taft Laboratory, Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Public Health Service, U.S. Department of Health and Human Services, 4676 Columbia Parkway, Cincinnati, OH 45226.

[3] We thank Dr. George Hutchison, Dr. Karl Shy, and Dr. Philip Enterline for their advice in the analysis and interpretation of the data. Dr. Thomas Smith for his guidance in estimating exposures, and Dr. Lynne Moody for her epidemiologic and editorial counsel. We also acknowledge the dedicated follow-up efforts of Mrs. Edith Dodd, Mrs. Clorinda Battaglia, Ms. Judy Edelbrock, Ms. Mary Hogan, and their staffs and the excellent assistance in manuscript preparation by Ms. Fran Guerra.

addition, to allow for internal comparisons, the study population was expanded to include 257 workers with brief (6-23 mo) employment and more complete ascertainment of workers with 2 or more years of employment. The total study population includes 602 white males.

BACKGROUND

The industrial plant under study has refined cadmium metals and cadmium compounds since 1925. It functioned previously as an arsenic smelter from 1918 to 1925 and as a lead smelter from 1886 to 1918. Although some cadmium processing operations were begun prior to 1925, the primary function of the plant for more than 50 years has been to recover cadmium and a number of other trace metals from "bag house" dust, a by-product of lead smelting. The facility is unusual in having a prolonged period of operation, with workers exposed predominantly to cadmium.

The industrial process recently was described by Smith et al. (*23*). Cadmium enters production principally as cadmium oxide dust (agglomerated fume). In a series of 10 physically isolated work areas, it is roasted, mixed with acid to form a cake, calcined, dissolved in water, recovered electrolytically, and treated further to produce cadmium oxide, metal, or yellow cadmium pigment. Air-monitoring data collected by the company from the 1940's to the present show that exposures differ substantially among departments and over time. Exposures have decreased over time due to the introduction of ventilation controls and to a mandatory respirator program introduced in the 1940's. Smith et al. (*23*) estimated the inhalation exposures that occurred in various departments (table 1). These estimates were based upon historical area monitoring data, adjusted to reflect the actual exposures of workers wearing respirators (*24*). Area-sampling data were first adjusted to reflect personal sampling, based on the ratio between area samples and personal exposure measurements from 1973 to 1976. For those departments and calendar periods in which workers wore respirators, the estimates of personal exposure were divided by 3.9, the geometric mean respirator protection factor measured in a survey at this plant in 1976 (*24*).

Also reflecting exposure are measurements of urine cadmium which the company obtained periodically on production workers since 1948. Urine samples were analyzed by colorimetric extraction until 1966 and subsequently by atomic absorption spectroscopy. Company records contained urine cadmium measurements for 261 members (43%) of the present cohort. These data are absent or extremely sparse for workers who left employment before 1960 and are representative only of production workers employed beyond 1960. Text-figure 1 shows the distribution of the median urine cadmium levels. These urine levels suggest a highly exposed population. They provide an index of group exposure but cannot be used to measure individual exposure because of the small number of samples for most workers (median of 2 samples/person; range, 0-79).

Few data are available on exposures other than cadmium at the smelter. Small quantities of high-purity lead, arsenic, thallium, and indium are produced sporadically by a few individuals in separate buildings. Some arsenic is evolved during cadmium recovery. An industrial hygiene survey conducted by NIOSH in 1973 found 0.3 and 1.1 μg arsenic/m^3 in the pre-melt department and 1.4 μg arsenic/m^3 in the retort department (*1*). These levels are substantially below the current OSHA 10 μg/m^3 PEL time-weighted average.

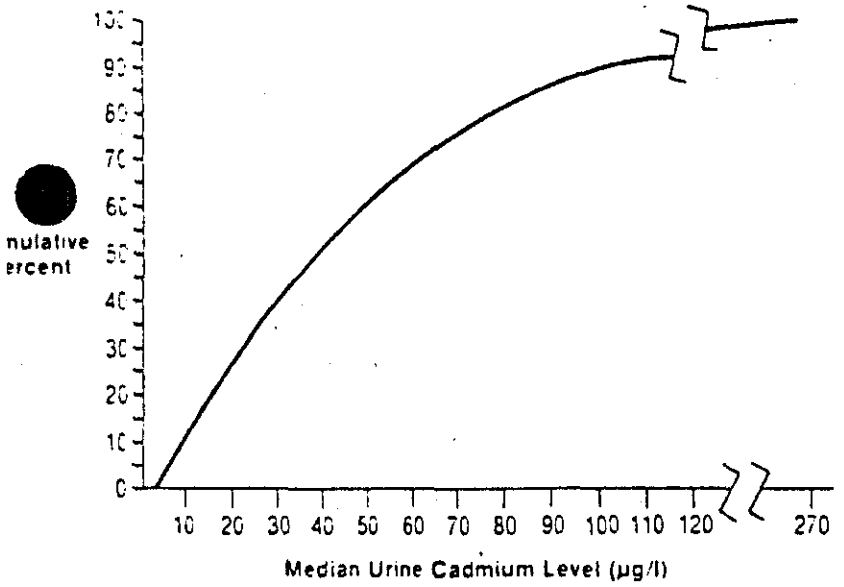
METHODS

The study population was defined from employment histories as recorded in the company personnel files. These records consist of a card for each employee and show the name, date of birth, social security number (since 1937), date of employment, date(s) of interruption of employment, and, in most cases, department or general work area for each period of employment. The records included retired and deceased as well as active employees. We enumerated all hourly employees and foremen who had worked a minimum of 6 months in a production area of the plant between January 1, 1940, and December 31, 1969. The requirement of production-area employment excluded several guards, office workers, and office area janitors who had been included in the Lemen et al. study (*1*). We also included production area foremen and a number of laborers whose records had been missing or whose employment histories had been inaccurately recorded and who thus had been omitted

TABLE 1.—*Estimates of cadmium inhalation exposures, by plant department and time period*[a]

Time period	Cadmium inhalation exposure, mg·m^{-3}, in:									
	Plant departments:									Offices[c] and laboratories
	Sampling	Roaster	Mixing	Calcine	Solution	Tank house[b]	Foundry	Retort	Pigment	
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950–54	0.6	0.6	0.4	1.5	0.8	0.04	0.1	0.2	0.2	0.01
1955–59	0.6	0.6	0.4	1.5	0.4	0.04	0.1	0.2	0.04	0.01
1960–64	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.04	0.007
1965–76	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.04	0.007

[a] Data from Smith et al. (*23*).
[b] Tank house estimates also were used for nonproduction plant departments that were not measured directly, e.g., the repair shops.
[c] Office estimates also were used for nonplant areas that were not measured directly, e.g., areas patrolled by the plant guard.



TEXT-FIGURE 1.—Cumulative distribution of median urine cadmium levels among 261 members of the cohort with at least one urine cadmium measurement. The median urine cadmium, in micrograms/liter, was computed for each worker for whom urine samples were available.

m the Lemen cohort. NIOSH identified the cohort ntly with a representative from the company and iewed the list with senior union officials.

For each worker, cumulative exposure to cadmium was culated according to length of employment and jobs thin the plant. Because many of the personnel records ecified general work categories rather than single partments, we categorized each period of a worker's ployment into one of 7 broad job categories; e.g., y 1 included production work in any of 6 "high"- e departments, including sampling, roasting and g house, mixing, calcine, foundry, and retort. Category ncluded production work in the solution, tank house, d pigment departments. The average exposure to borne cadmium for each of these composite categories is calculated on the basis of the industrial hygiene data table 1 (*23*), with each department contributing to a ighted average according to the proportion of workers ually employed there. Each worker's cumulative expore over time was computed as the sum of the number of ys worked in a given job category multiplied by the erage inhalation exposure of that category for the levant time period. Cumulative exposure was expressed milligram days per cubic meter (mg-days/m^3).

The vital status of all workers in the cohort was ermined as of December 31, 1978. Follow-up produres used the records of the Social Security Administran, of the state vital statistics offices, and of the mpany and union and direct telephoning. Death rtificates were obtained for persons known to be ceased and were coded by a qualified nosologist cording to the protocol of the ICD revision in effect at e time of death. The codes were subsequently converted the seventh revision codes for the analysis (*25*). Under e rules of this and subsequent revisions, cancer is coded the underlying cause of death if the immediate cause of "unmistakably a direct sequel of" the malignant . Deceased workers for whom no death certificate has yet been located were assumed dead on the date specified by the reporting agency, with cause of death unknown. Persons lost to follow-up were assumed to be alive—which might possibly result in overestimation of cause-specific expected deaths.

The mortality experience of the cohort was analyzed with the use of a modified life-table system developed by NIOSH (*25*). In this system, a worker accumulates PYAR upon completion of the eligibility period (in this study, at 6 months of employment). The PYAR are specific for 5-year age groups, calendar periods, and years since first employment (latency). An expected number of deaths is calculated by multiplying U.S. white male death rates by the corresponding age and calendar-year PYAR categories. The resulting quantities are summed over all ages and years to obtain the total expected numbers. The observed numbers of cause-specific deaths are compared with the numbers expected. The ratio of observed-to-expected deaths multiplied by 100 is expressed as the SMR.

In the initial analysis, in which mortality in the cadmium workers was compared to that of the general U.S. white male population, the causes for which excess mortality or morbidity were observed in previous studies of cadmium workers were considered a priori to be of particular interest. Those of central concern included deaths from prostate and lung cancers (*1*, *20*) and from nonmalignant respiratory and renal diseases (*6*, *15*, *16*). Other conditions for which a priori concern has been raised include hypertension (*6*, *26*) and renal cancer (*27*). Mortality from NMGID also was examined because of the acute gastrointestinal toxicity of cadmium and because of reports of chronic gastritis and gastrointestinal ulceration (*28–30*). Although in each case cadmium is suspected of causing an excess of mortality, we present 95% CI, corresponding to a two-sided alpha level of 0.05, throughout this paper. Where the 95% CI includes the null but the 90% does not, we present both. CI were

TABLE 2.—*Vital status of white male cadmium production workers, by employment duration*

Worker status	Workers, No. (%), employed:		
	6–23 mo	2+ yr	Total
Alive	189 (74)	222 (64)	411 (69)
Dead	60 (23)	119 (35)	179 (29)
Lost to follow-up	8 (3)	4 (1)	12 (2)
Total	257	345	602

calculated with the use of Fisher's exact CI (if either the observed or expected was less than 10) or approximate CI (if observed or expected frequencies were 10 or more) (*31*).

For selected causes of death we examined mortality in relation to cumulative exposure to cadmium. For subgroup comparisons we used the directly standardized SRR as the measure of effect (*32*). To compute these, the age-specific and calendar time-specific rates of the subgroup were multiplied by the corresponding PYAR cells of the standard population—here the PYAR distribution of the overall cadmium cohort. The results were summed to yield the expected number of deaths that would occur in the overall cohort were the rates of the subgroup to apply. This total number of expected deaths was divided by the total number of PYAR in the overall cohort to yield a directly standardized mortality rate. The ratio of this rate to the standardized rate for the overall cohort, if U.S. age, sex, race, and calendar-period rates applied, yielded the SRR.

To analyze mortality by cumulative exposure, we chose the exposure categories a priori, on the basis of current or proposed regulatory standards and on the assumption that such standards are intended to protect a worker over a 40-year working lifetime; e.g., 40 years' exposure to cadmium at or below the current NIOSH proposed TWA of 40 $\mu g/m^3$ would result in a cumulative exposure of up to 584 mg-days/m^3. Forty years' exposure to cadmium at levels above the current NIOSH TWA, but within the current OSHA 200 $\mu g/m^3$ PEL, would result in a cumulative exposure of up to 2,920 mg-days/m^3.

RESULTS

Because of the small number of nonwhites and females (total = 13) in the cohort, we restricted the analysis to the 602 white males. Table 2 shows the vital status of these workers, by duration of employment, as of December 31, 1978. Of these, 411 were alive, 179 were dead, and 12 (2.0%) had unknown vital status; 43% had been employed for less than 2 years.

Text-figure 2 shows the distribution of the cohort by year of first employment. Two-thirds of the individuals had started work before 1949 and thus could be followed beyond 30 years. Nearly 83% had over 20 years of follow-up.

Table 3 compares the number of cause-specific deaths among the overall cohort with the number expected, based on U.S. rates. A deficit was observed in mortality from all causes (SMR = 95; 95% CI = 81–110), due to a deficit in diseases of the circulatory system (SMR = 65; 95% CI = 49–85). Significantly increased mortality was observed for respiratory cancer and NMGID. The excess of nonmalignant respiratory disease was not statistically significant in the overall cohort.

Twenty deaths were due to respiratory cancer, all among workers with over 2 years' employment and all due to cancers of the lung, trachea, and bronchus. Expected deaths were 11.43 in this more specific subgroup (ICD code 162–163), which was subsequently called lung cancer. Two of the deaths from lung cancer were initially miscoded as being due to other causes. Inasmuch as the immediate causes of these 2 deaths were unmistakably direct sequels of malignant conditions, the deaths were recoded to lung cancer in accordance with the rules of the ICD Seventh Revision. Analysis that excluded these cases yielded an SMR for lung cancer of 157 (18 Obs vs. 11.43 Exp; 95% CI = 93–249; 90% CI = 102–234).

TEXT-FIGURE 2.—Cumulative distribution by year of first employment for cadmium production workers included in cohort.

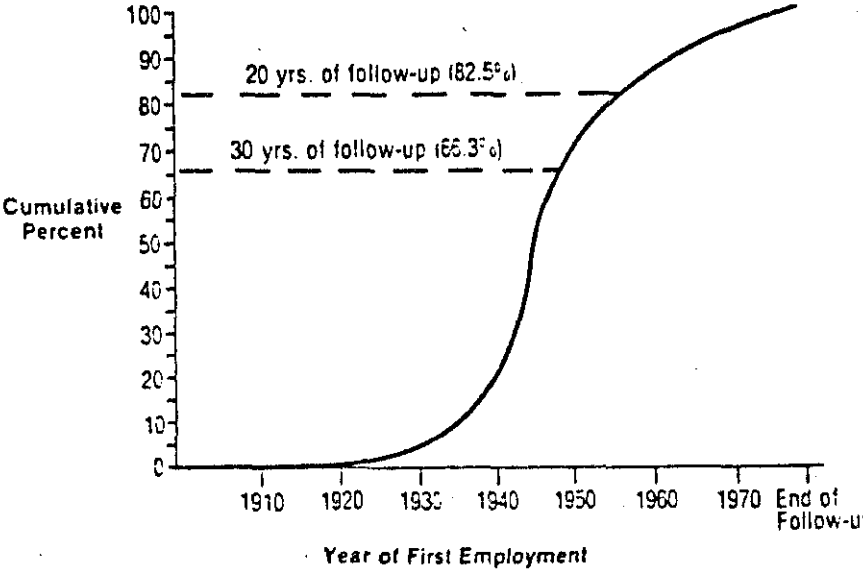


TABLE 3 —*Mortality from selected causes of death among white males with 6 or more months of cadmium production work: 1940–69*

Cause of death	ICD, 7th revision	No. of deaths		SMR	95% CI
		Obs	Exp		
Malignant neoplasm	140–199	41	36.46	112	81–153
Digestive system	150–159	7	10.85	65	26–133
Respiratory system	160–164	20	12.15	165	101–254
Genitourinary tract	177–182	6	4.45	135	49–293
Lymphatic and hematopoietic tissues	200–205	3	3.37	89	17–270
Other unspecified neoplasms		5	5.64	89	29–207
Diseases of the circulatory system: Heart disease	400–468	56	85.68	65	49–85
Nonmalignant respiratory diseases	470–493. 500–527	16	10.37	154	88–251
Acute infections, influenza, pneumonia	470–493	7	4.47	157	63–323
Other respiratory diseases	500–527	9	5.90	153	69–290
NMGID	540–543. 560–561. 570	9	2.35	383	175–727
All other causes	—	57	54.01	106	80–137
All causes of death	—	179	188.87	95	81–110

Of the 6 deaths from genitourinary cancer, 1 was due to renal cancer (vs. 0.92 Exp), 2 to cancers of the bladder and other urinary organs (vs. 1.10 Exp), and 3 to prostate cancer (vs. 2.20 Exp). No new deaths from prostate cancer were observed since the Lemen et al. report (*1*).

One of the original prostate cases was a plant guard who was excluded from this cohort because he had not worked 6 months in a production area. Another deceased worker had prostate cancer listed as a contributing cause of death but could not be included in this analysis because prostate cancer was not listed as the underlying cause of death. The remaining 3 deaths from prostate cancer had occurred among workers with 2 or more years of employment and 20 or more years of observation (vs. 1.41 Exp; SMR=213; 95% CI=44–622).

Sixteen deaths occurred due to nonmalignant respiratory disease; 7 of these involved workers employed for less than 2 years. The death certificates of 3 workers mentioned silicosis. Silica exposure may have occurred from work with refractory brick in furnace areas of the plant but is undocumented. One of the workers whose certificate mentioned advanced silicosis had been employed for only 1 year, suggesting that the exposure had occurred elsewhere.

We noted 9 deaths from NMGID, excluding cirrhosis. The death certificates of 6 of these suggested peptic ulcer disease. Most of the deaths from NMGID were of long-term employees, whereas 5 of the 6 deaths attributed to cirrhosis involved short-term workers.

No excesses were noted for deaths attributable to hypertension (3 Obs; 3.22 Exp) or to nonmalignant renal disease (1 Obs; 1.35 Exp). A single death certificate listed renal disease as the underlying cause of death [death had been due to acute nephritis (ICD code 590)], and 4 other certificates listed nonmalignant renal disease as a contributing cause of death. No comparison rates were available for analysis of these contributing causes of death.

Arsenic Exposure

Substantial arsenic exposure occurred throughout the plant during the years 1918–25 when the facility functioned as an arsenic smelter. Because arsenic is a known risk factor for lung cancer (*33*), we stratified the cohort into workers employed before and those first employed on or after January 1, 1926. We then compared mortality from lung cancer among each of these subgroups with that of U.S. white males (table 4). Lung cancer mortality was significantly elevated among persons hired prior to January 1, 1926. Among workers hired after that date, the excess of lung cancer deaths was statistically significant among workers employed for 2 or more years. When the 2 initially miscoded deaths from lung cancer are excluded from this analysis, mortality from lung cancer remains statistically above that expected both for workers hired prior to 1926 (Obs=3; Exp=0.56; 95% CI=110–1565) and for workers with 2 or more years' employment who had been hired after 1926 (Obs=15; Exp=7.0; 95% CI=120–353).

Mortality by Cumulative Exposure to Cadmium

Tables 5 and 6 present data on mortality from lung cancer and NMGID in relation to cumulative exposure to

TABLE 4.—*Mortality from lung cancer (ICD 162–163) in white male cadmium production workers, by date of hire*

Worker employment status	No. of deaths		SMR	95% CI
	Obs	Exp		
Hired prior to January 1, 1926	4	0.56	714	195–1829
Hired on or after January 1, 1926				
Overall cohort	16	10.87	147	84–239
≥2 years employment	16	7.00	229	131–371

cadmium. Only the 576 workers hired on or after January 1, 1926, are included in these analyses. Lung cancer mortality increased with increasing cumulative exposure to cadmium, and this trend was apparent both in the SRR and the SMR. A similar pattern was seen when the analysis was restricted to workers with 20 or more years since first exposure. The regression slope for the SRR for lung cancer (table 5) was 7.33×10^{-7} ($P=.0001$). The excess of deaths from lung cancer was statistically significant only for the stratum of workers whose cumulative exposure to cadmium exceeded 2,920 mg-days/m^3, the level corresponding to a 40-year exposure above the current OSHA limit (95% CI for the SMR = 113-577). In a separate analysis (not shown), workers whose cumulative exposure to cadmium ranged from 293 to 584 mg-days/m^3 showed an SMR for lung cancer of 100 and an SRR of 0.96. This level of cumulative exposure is equivalent to 40 years' exposure to airborne cadmium at levels between 21 and 40 μg/m^3. In contrast to its relationship with cumulative exposure, the excess of lung cancer mortality did not increase with length of employment beyond 2 years. Workers employed for 2-9 years, 10-19 years, and 20 or more years all showed approximately twice the number of deaths from lung cancer as expected from the U.S. rates.

Only 6 deaths from NMGID occurred among workers hired since 1926. A statistically significant upward trend was evident in the SRR when mortality from NMGID was analyzed by cumulative exposure (slope $=2.73\times10^{-7}$; $P=.014$). Because of the small number of cases of NMGID, these estimates are less stable than those for lung cancer. Three additional deaths from NMGID occurred among the 26 workers hired before 1926. If arsenic were unrelated to NMGID, these deaths would increase further the observed mortality in the high-exposure, long-term employment subgroup.

A similar analysis of deaths from nonmalignant respiratory disease was not performed, inasmuch as this study found no significant excess of deaths from this cause either in the overall cohort or among workers with 2 or more years of employment. An excess of deaths in this category was apparent, however, among workers employed for 6 months to 2 years (Obs = 8; Exp = 3.2; SMR = 249; 95% CI = 108-491). One of these deaths was attributable to silicosis.

TABLE 5.—*Lung cancer (ICD 162-163) mortality, by cumulative exposure to cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent*	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7,005	2	53	0.48
585-2,920†	41-200 μg/m^3	5,825	7	152	1.55
≥2,921	≥200 μg/m^3	2,214	7	280	3.45
U.S. white males		—	—	100	1.00

*The TWA that over a 40-year working lifetime would result in the indicated cumulative exposure.

†Exclusion of the single worker hired after 1926, whose death from lung cancer was initially miscoded, reduces the number of observed deaths in this stratum to 6 and the SRR to 1.34.

TABLE 6.—*NMGID (ICD 540-43, 560-61, and 570) mortality, by cumulative exposure to airborne cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent*	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7,005	2	300	4.8
585-2,920	41-200 μg/m^3	5,825	1	112	1.0
≥2,921	≥200 μg/m^3	2,214	3	582	11.3
U.S. white males		—	—	100	1.00

*The TWA that over a 40-yr working lifetime would result in the indicated cumulative exposure.

DISCUSSION

The findings of principal interest in this study were the increased mortality from lung cancer among workers employed for 2 or more years and the dose-response relationship between lung cancer mortality and cumulative exposure to cadmium. The excess of malignant respiratory disease, noted previously in this cohort by Lemen et al. (*1*), has continued during the expanded observation period. Eight new deaths from lung cancer have been identified. The excess of deaths from respiratory cancer among workers with 2 or more years of employment continues to be statistically significant (new cases = 8; Exp = 2.94; SMR = 272; 95% CI = 117-536). Furthermore, because national death rates for respiratory cancer overestimate regional (State of Colorado and Denver County) rates by 10-25% (*34*), the measured excess of lung cancer deaths among longer-term employees probably underestimates the actual increase.

The observed excess of deaths from respiratory cancer could be due to a true causal relationship between cadmium and lung cancer, to bias (the effect of uncontrolled confounding), or to chance. Cigarette smoking and exposure to arsenic are two extraneous factors which, if uncontrolled in the analysis, could explain the findings. Although the tobacco smoking habits of these cadmium workers were not recorded at the time of employment, company representatives did collect information on past tobacco use by mailing a questionnaire to members of the cohort in 1982 (*35*). Interviews with approximately 70% of survivors or next of kin showed that 77.5% of those for whom information was gathered were current or former smokers. This prevalence of "ever smokers" resembles the 72.9% prevalence noted among U.S. white males, age 20 or over, in the 1965 HIS (*36*). The 1965 HIS is perhaps the best source of information on the smoking habits of the general population during the observation period of this study. Using the 1965 survey data, one can estimate the effect that disproportionately heavy smoking by the cadmium workers would have on lung cancer mortality relative to that of the general population. Computations developed by Axelson (*37*) and Blair and Spiritas (*38*), combined with the HIS

data, show that even an assumed doubling of the proportion of heavy smokers will have only a small effect on the rate ratio for lung cancer; e.g., if 40% of the cadmium workers smoked more than 25 cigarettes/day, compared to 20% of the 1965 white male general population, the rate ratio would increase only 1.25-fold. Thus cigarette smoking alone is unlikely to account for the twofold-to-threefold increase in deaths from lung cancer observed among workers in this cohort who had had 2 or more years of employment.

Substantial and widespread arsenic exposure occurred prior to 1926 when the plant operated as an arsenic smelter. The rate of lung cancer mortality among the 26 workers employed before 1926 was nearly six times the U.S. rates. Even after 1925, a small and unspecified number of workers occasionally processed arsenic in one area of the plant. This was an intermittent operation, apparently staffed by workers from the roasting area, and lasted into the 1930's. A second and continuing source of exposure involved workers in the sampling, mixing, roasting, and calcine furnace areas of the plant who were exposed to arsenic contamination from the incoming feed material. Only six industrial hygiene measurements were made in these areas before 1975. In 1950, airborne arsenic concentrations ranged from 300 to 700 $\mu g/m^3$ near the roasting and calcine furnaces, the areas of highest exposure. Measurements by the company and OSHA in 1979 show that arsenic exposures in these areas had decreased to about 100 $\mu g/m^3$. Although air levels of arsenic in this confined area were still 10 times higher than the legal OSHA threshold limit value of 10 $\mu g/m^3$, actual personal exposures were lower due to respirator usage. One can estimate the number of lung cancer deaths potentially attributable to arsenic by assuming *a*) an average airborne arsenic exposure of 500 $\mu g/m^3$ in the "high-arsenic" work areas during the years of this study, *b*) a respirator protection factor of 75% (similar to that assumed for cadmium), and *c*) an estimated 20% of PY of exposure spent in high-arsenic jobs, an estimate based on personnel and biologic monitoring data. On the basis of these assumptions, the average airborne arsenic exposure of persons in this study would have been 25 $\mu g/m^3$. Inasmuch as the 576 workers hired after 1926 were employed an average of 3 years, they acquired 1,728 PY of exposure to 25 $\mu g/m^3$. Such an exposure should result in no more than 0.77 lung cancers, on the basis of a risk assessment model for arsenic developed by the OSHA (*39*).

Although the estimate of an average air exposure to arsenic of 25 $\mu g/m^3$ rests on several assumptions, it is more likely to overestimate than to underestimate actual exposures. Only a fraction of jobs in the high-arsenic areas involved exposures as high as those of the furnace areas. High-exposure jobs in the roaster area were frequently staffed by entry-level workers, many of whom worked less than 6 months. These very short-term workers with brief but high exposure were excluded from the mortality study, yet they were included in our estimate of 20% of PY of exposure spent in high-arsenic jobs. In addition, urinary arsenic levels measured on workers in the high arsenic areas from 1960 to 1980 averaged only 46 μg/liter, a level consistent with an average inhaled arsenic concentration of 14 $\mu g/m^3$ (*40*). Thus the assumption of an average inhaled concentration of 125 $\mu g/m^3$ (25% of 500 $\mu g/m^3$) over these years overestimates the actual exposures by ninefold, more than compensating for the unquantified higher exposures during the early years. Arsenic alone does not appear to explain the observed excess of deaths from lung cancer.

The central finding of the study was the observed dose-response relationship between mortality from lung cancer and cumulative exposure to cadmium. Previous epidemiologic studies of cadmium workers have had insufficient industrial hygiene data to estimate cumulative exposure. The strong dose-response pattern observed in this study is consistent with a causal relationship between cadmium and lung cancer. It also suggests that the current OSHA occupational standard, limiting exposure to cadmium dust to 200 $\mu g/m^3$, is inadequate to protect workers over a 40-year working lifetime. Workers whose cumulative exposure was below the 40-year equivalent of the NIOSH-recommended TWA of 40 $\mu g/m^3$ showed no excess of lung cancer deaths, whereas workers whose cumulative exposure was within the current OSHA limit but above the NIOSH recommended limit showed a 50% excess in lung cancer deaths.

The potential role of cadmium as a pulmonary carcinogen has gained biologic plausibility because of the experimental induction of lung cancer in rats exposed to cadmium chloride aerosol (*22*). Epidemiologic studies of mortality among cadmium workers in England and Sweden have, however, shown conflicting results. Sorahan and Waterhouse (*18*) found a statistically significant excess of deaths from respiratory cancer (Obs=89; Exp=70.2; SMR=127; 90% CI=106-151) in a cohort of 3,025 English nickel-cadmium battery workers. A subset of these workers had been included in the earlier studies of Potts (*2*) and Kipling and Waterhouse (*3*). Although the authors observed a positive association between death from respiratory cancer and cumulative duration of employment in jobs with high or moderate exposure to cadmium, they noted that these workers also were exposed potentially to oxyacetylene welding fumes and to nickel hydroxide dust. Holden (*17*) found a statistically significant excess of deaths from respiratory cancer (Obs=36; Exp=26.06; SMR=138; 95% CI=108-339) and from prostate cancer (Obs=8; Exp=3.00; SMR=267; 90% CI=115-525) among 624 cadmium "vicinity" workers but not among 347 workers employed directly in manufacturing cadmium copper alloys. The vicinity workers were also exposed to arsenic.

Armstrong and Kazantzis (*19*), excluding the cohorts studied by Sorahan and Waterhouse (*18*) and Holden (*17*), recently described mortality among workers enrolled in the registry of English cadmium workers. A small, statistically insignificant excess of deaths from respiratory cancer was evident in the overall cohort (Obs=199; Exp=185.6; SMR=107; 95% CI=92-122). This marginal excess is consistent with the results in our study, inasmuch as most of the workers in the Armstrong cohort

had only minimal exposure to cadmium. Less than 3% of the workers in the Armstrong cohort were classified as "ever highly exposed." High exposure was defined as having worked at least 1 year in a job that the authors judged would produce a urine cadmium level of at least 20 μg/liter following chronic exposure. In our cohort, 81% of workers for whom urine cadmium had been measured had a median urine cadmium of at least 20 μg/liter. Even among workers with less than 2 years of employment, approximately 30% had a median urine level of 20 μg/liter. One might argue that in each of the epidemiologic studies in which excess mortality from lung cancer was seen, other occupational exposures such as arsenic or nickel were present and could have contributed to the problem. Unfortunately, the published versions of these studies do not include sufficient information on the level of exposure to either cadmium or to other metals to permit assessment of this problem.

Increased mortality from NMGID has not been reported previously in association with cadmium. Ingested cadmium is a severe gastrointestinal irritant in man (*5*, *28*), and Tsuji et al. (*29*) and Adams et al. (*30*) have commented on the frequent observation of gastritis and gastrointestinal ulceration among chronically exposed persons. In our study we observed a 2.8-fold overall increase in deaths from NMGID (excluding cirrhosis of the liver) among workers employed on or after January 1, 1926. Deaths from these causes showed a general association with prolonged employment. Because NMGID previously has not been examined systematically, we view this finding as a hypothesis to be examined further in future studies rather than as a definitive conclusion.

No new deaths from prostate cancer have occurred in this cohort since the Lemen study (*1*). In addition, 1 of the 4 original cases was excluded from this analysis because of the revised definition of the cohort. The excluded worker had been employed for 18 years as a guard who patrolled the entire plant but at no time had worked for 6 months in a production area. Exclusion of such a worker is to a certain extent arbitrary. Also, because the small size and short additional follow-up of this cohort has low statistical power, and because prostate cancer is frequently a nonfatal disease imperfectly studied by death certificate data, we believe that the absence of new cases during the 5 additional years of follow-up weakens but does not refute the possible association between cadmium and prostate cancer.

The presence of only 1 death attributed to chronic renal failure is interesting, inasmuch as cadmium is a known nephrotoxin and because increased mortality from chronic nephritis and nephrosis has been noted among Swedish battery workers (*15*, *16*). The difference may well be due to local differences in recording certain types of information on death certificates. The comparisons in our study were based upon the underlying causes of death and ignore the data for 4 individuals for whom renal disease was noted as a contributing cause of death. Impaired renal function frequently is underreported on death certificates, even when the disease was sufficiently severe to require chronic hemodialysis (*41*).

In contrast to the Lemen study (*1*), we found no excess of deaths from nonmalignant respiratory disease either in the overall cohort or among workers with 2 or more years of employment. If deaths from silicosis are excluded, the only increase in mortality from these causes is among workers with short-term employment. The significance of this finding is unclear.

In summary, the finding of increased lung cancer mortality in this follow-up analysis is consistent 1) with the previous mortality study of this cohort (*1*), 2) with the recently published rat inhalation study (*13*), and 3) with the epidemiologic findings of Sorahan and Waterhouse (*18*). An association of cadmium with NMGID was also observed. Previous findings (*1-3*) of prostate cancer among exposed workers were somewhat weakened.

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Metallothionein
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FUNCTIONS OF HEPATIC AND RENAL METALLOTHIONEINS IN THE CONTROL OF THE METABOLISM OF CADMIUM AND CERTAIN OTHER BIVALENT CATIONS

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As the first metallothionein to be isolated (1) contained a high content of Cd^{2+}, it was a logical assumption that one function of thionein might be to provide a defence mechanism against this toxic cation. This possibility, amongst others, was considered by Kägi and Vallee (2,3) and was developed by Piscator (4) as an hypothesis to explain the progressive accumulation of biologically inert Cd^{2+} in the livers and kidneys of rabbits, exposed to repeated small doses of $CdCl_2$. The detoxification function of thionein against low level exposure to either parenterally, or orally, administered Cd^{2+}, was confirmed in a number of later investigations (5-10, see also ref.11). These investigations established clearly that much of the high body burden of Cd^{2+} accumulated by the experimental animal under these conditions was present as the metallothionein in the livers and kidneys, and thus was unavailable for interaction with processes with important biological functions. Other studies suggested that the inducible synthesis of thionein in these organs is not limited to Cd^{2+}, but probably functions under conditions of either chronic exposure to Hg^{2+} (12), or increased tissue concentrations of the essential, but potentially toxic, Zn^{2+} and Cu^{2+} cations (e.g. refs. 13 & 14).

Pretreatment of experimental animals with a low dose of Cd^{2+}, or higher dose of Zn^{2+}, is known to protect them against a subsequent, normally lethal, dose of Cd^{2+} (15) and also to prevent the Cd^{2+}-induced testicular damage (16,17), placental haemorrhage (18) and foetal malformations (19-21). As both pretreatment cations stimulate the synthesis of the corresponding metallothioneins, protection against such acute effects of Cd^{2+} also has been attributed to these metalloproteins (6,8,22-25). Since Zn^{2+} is a common component of the metallothioneins that are induced by both Cd^{2+} and Zn^{2+}, it is possible that such protection could result from the replacement of this cation by Cd^{2+}. Alternatively, pretreatment might eliminate the lag in thionein synthesis (26), such that further production of the protein is an immediate response to subsequent challenge with Cd^{2+}. There is some experimental support for both of these possibilities. Thus Cd^{2+} has been shown to displace Zn^{2+} from zinc-thionein (7,8) and from (cadmium, zinc)-thionein (22,24), in the livers of animals pretreated with Zn^{2+} and Cd^{2+} respectively. Yoshikawa (27) and Suzuki and Yoshikawa (22) consider that this

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replacement of Zn^{2+} in presynthesized (cadmium, zinc)-thionein leads to a more rapid accumulation and immobilization of Cd^{2+} in the liver of the pretreated animal and, as a result of this, uptake of the cation by other organs is decreased. According to Leber and Miya (24) the hepatic concentration of (cadmium, zinc)-thionein in mice, and thus of replaceable Zn^{2+}, increases with the pretreatment dose, as does the tolerance to Cd^{2+} on subsequent exposure. A positive correlation between the hepatic content of this metallothionein and the LD_{50} of Cd^{2+} in mice after pretreatment with different doses of the cation also has been reported by Probst et al. (25). Treatment of rats with an oral dose of Cd^{2+} (20 mg/kg) was found by Squibb et al. (23) to protect against a second (100 mg Cd^{2+}/kg), given after 24h. and to increase the uptake of Cd^{2+} not only in the liver, but also in the kidneys and testes (cf. Yoshikawa (27), Suzuki and Yoshikawa (28)). In non-pretreated (control) animals, hepatic thionein synthesis exhibited the usual lag and thus, during the first few hours after the oral administration of Cd^{2+} (100 mg/kg), most of the cation that was taken up by the liver was associated with the high molecular weight proteins of the cytosol. In the pretreated animals, however, the lag phase was eliminated and, from the earliest times after the administration of the second dose, all of the Cd^{2+} in the soluble fraction of the liver was bound to thionein (23).

Whilst these investigations seem to support the concept of a protective function of pre-induced (cadmium, zinc)-thionein against the acute toxicity of Cd^{2+} there are other observations which are difficult to reeoncile with this view. For example, protection can be obtained with, and is effective against, other cations that do not induce thionein synthesis. Thus In^{3+} and Mn^{2+} protect against acute doses of Cd^{2+} (28), and pretreatment with Pb^{2+} confers protection against toxic doses of Pb^{2+} (29). Also, protection against Cd^{2+} in rats has been shown to be maximal 1-3 days after pretreatment with a low dose of Cd^{2+} and then to decrease with time (30). Both the content of the pre-induced metallothionein, as well as the capacity for the immediate synthesis of this metalloprotein, however, were retained in the liver of the pretreated animal for a much longer period. In agreement with the observations of Yoshikawa (27), Suzuki and Yoshikawa (22), Squibb et al. (23), and Cherian and Vostal (31), hepatic uptake of Cd^{2+} was found to be much greater in the pretreated animals than in the non-pretreated controls. Uptake of the cation by the kidney, spleen, pancreas, brain and heart, however, was unaltered, whilst faecal excretion was decreased. The increased retention in the liver, therefore, probably was due to decreased biliary excretion of Cd^{2+} that is known to result from pretreatment (31).

The synthesis of hepatic zinc-thionein is stimulated by restriction of food intake (32), but Webb and Verschoyle (31) have shown that the intravenous LD_{50} of Cd^{2+} in starved rats is the same as that in normally fed animals. Also, even though weanling rats contain very high concentrations of zinc-thionein in their livers, the LD_{50} of intraperitoneally administered Cd^{2+} is not significantly different from that in adult females (G.P. Samarawickrama and M. Webb, unpublished observations).

The above discussion suggests, therefore, that the acute toxicity of Cd^{2+} is not determined by the hepatic concentration of presynthesized zinc-, or (cadmium, zinc)-thionein. Webb and Magos (33) also conclude that the presence of the latter metallothionein in the kidneys of Cd^{2+}-pretreated rats cannot explain the resistance of these animals to normally nephrotoxic doses of Hg^{2+}. In this work, for example, Cd^{2+}-pretreatment was found to increase not only the renal content of thionein-bound-Hg^{2+}, as observed previously by Suzuki (34) and Shaikh et al. (35), but also the contents of Hg^{2+} in other cellular components. As, at normally nephrotoxic doses, increased Hg^{2+}-incorporation into these components was greater than that into the metallothionein, it seems that there is no obvious reason to attribute the protective effect of Cd^{2+} to the induction of thionein synthesis, and other mechanisms (cf. e.g. 36) seem more probable.

Whilst, therefore, a role for thionein in the detoxification of certain heavy metal ions seems to be established clearly only at continuous low level exposure, this is unlikely to be the normal physiological function of the protein. It has been suggested that either thionein itself (37), or its copper derivative (38), may be the biologically active molecule with functions in the maintenance of redox potentials (37), ion transport (37), metabolic pools of cysteine residues (39), and in bioenergetic systems, particularly when the contents of cytochrome c oxidase are low (38). There is also much evidence that the primary biological function of this inducible protein is related to the metabolism of the essential Zn^{2+} cation (7,8,32,40-44). According to Chen et al. (43,45), zinc-thionein, which accumulates in the livers of rats that are maintained on a diet with high levels of Zn^{2+}, is eliminated within 3 days when the animals are transferred to a Zn^{2+}-deficient diet, the loss being associated with increased urinary and faecal excretion of low molecular weight Zn^{2+} complexes. They conclude, therefore, that thionein has a fundamental role in the accumulation of excess Zn^{2+}, rather than in the storage of the cation for subsequent utilization. A conservation function, however, is indicated by the formation of hepatic zinc-thionein in the rat during post-surgical trauma (46) and in response to starvation (32,44).

Regulation of Zn^{2+} absorption in rats, attributed by Cotzias et al. (47) to negative-feedback control, was shown by Evans et al. (48) to be mediated, at least in part, by the Zn^{2+}-content of the intestinal mucosa which, in turn, is regulated by the Zn^{2+}-concentration of the plasma. Previously a function of thionein in the regulation of the absorption and/or transport of both Zn^{2+} and Cu^{2+} seemed to have been established by the isolation of metalloproteins, tentatively identified as zinc- and copper-thioneins from the intestinal mucosa of the chick (49), rat (50) and bovine (51). Later work by Evans and collaborators (48,52-55), however, established that Zn^{2+}-absorption is determined not by the formation of zinc-thionein, which is absent from the intestinal mucosa of the rat when the rate of absorption is high, but by a low molecular weight peptide (55), that acts as a ligand for Zn^{2+} in the mucosa, and the degree of saturation of the cation-binding sites of the carrier protein, albumin (53,56), or transferrin (57), in serum. This work was confirmed and extended by Richards and Cousins (44,58,59) who produced evidence that absorption of Zn^{2+} in the rat was related directly to the presence in the intestinal mucosa of the Zn^{2+}-chelate of the low molecular weight ligand and inversely to the synthesis of zinc-thionein. These authors suggest that, in cells of both the liver and intestinal mucosa, the contents of this metallothionein are correlated with the serum Zn^{2+}-concentration; in the former, synthesis of zinc-thionein is considered to control uptake and storage of Zn^{2+} and, in the latter, to form an alternative cation-binding species, which acts competitively with the Zn^{2+}-carrier peptide to regulate the transfer of the cation to the blood.

At present, there are difficulties in the application of this regulatory hypothesis to the pregnant animal, in which transfer of Zn^{2+} from the mother to the foetus must be related to the Zn^{2+}-concentration in the maternal blood. As was observed initially by Kägi (60), metallothioneins seem to be present in large amounts in certain foetal tissues. High concentrations of zinc-thionein, for example, occur in the livers of foetal rats (61, G.P. Samarawickrama and M. Webb, unpublished observations) rabbits and human-beings (A. Bakka and M. Webb, unpublished observations), and of (copper,zinc)-thioneins in the livers of murine (A. Bakka and M. Webb, unpublished observations), bovine (62) and probably porcine (63) foetuses. In the liver of the foetal rat, the concentration of thionein-bound-Zn^{2+} may exceed 70 μg/g wet wt. tissue and yet be at or near the limit of detection by conventional methods of analysis in the maternal liver (G.P. Samarawickrama and M. Webb, unpublished observations). Although the variability in cation contents of different foetal metallothioneins might be considered to be indicative of a storage or protective role, there is some

evidence to suggest that hepatic zinc-thionein of the rat foetus, at least, may be of functional significance (A. Bakka, G.P. Samarawickrama and M. Webb, unpublished observations). Thus, in these foetal livers, the content of thionein-bound-Zn^{2+} increases rapidly from the 16th day of gestation and, at birth, may be between 70 and 100 μg/g wet wt. tissue. After birth, the hepatic concentration of the metallothionein at first increases, but at a slower rate, to a maximum at about 7 days. It then falls almost to zero at 18 days. Intravenous administration of Cd^{2+} (1.25 mg/kg) to the pregnant rat on the 16th day of gestation prevents subsequent accumulation of zinc-thionein in the foetal livers. This seems to be due to the inhibition of Zn^{2+}-transport by Cd^{2+} in the maternal placenta, and not to the small amount of the latter cation that enters the foetus at this dose level, and which is bound by the metallo-thionein of the foetal liver. Inhibition of Zn^{2+}-transport persists for the remainder of gestation, although it decreases slowly (e.g. from 84% at 4h. after Cd^{2+}-administration to 66% at 48h.) with time.

If accumulation of zinc-thionein provides a defence mechanism against excess Zn^{2+} during normal foetal development, the content of the metalloprotein might be expected to remain low in the livers of the newborn pups of the Cd^{2+}-treated mothers. In these litters, however, the hepatic concentration of zinc-thionein increases to reach approximately the same maximum (60–80 μg thionein-bound-Zn^{2+}/g wet wt. tissue) at the same age as that in normal newborn animals. Fractionation of the liver cytosol of the weanling animal shows that, once the content of hepatic zinc-thionein reaches its maximum and begins to decrease, the contents of both Zn^{2+} and protein in one of the high molecular weight fractions increase. The gain in Zn^{2+} by this heterogeneous fraction which, as shown originally by Bremner and Marshall (64) and Bremner and Davies (46), contains super-oxide dismutase and carbonic anhydrase, is not stoichiometric with the loss from the metallothionein; an observation that possibly is to be expected from the findings of Chen *et al.* (43,45) on the elimination of thionein-bound-Zn^{2+} from the liver of the Zn^{2+}-loaded adult rat. These results, therefore, indicate but, at present, provide no firm evidence to support, the possi-bility that accumulation of hepatic zinc-thionein during late foetal and early post-natal life in the rat may be related to subsequent requirements for the cation in the synthesis of other metalloproteins at later stages of development. Such a function has been considered previously for neonatal mitochondrocuprein (65), which is regarded as a polymeric form of partially loaded copper-thionein (65,66), and may act as a reservoir of Cu^{2+} for the subsequent formation of cytochrome-c oxidase, the content of which increases rapidly during the neonatal period.

It is possible that, if copper-thionein undergoes polymerization in vivo to mitochondrocuprein, the presence of zinc-thionein in some foetal livers, and of (copper, zinc)-thionein in others, may be correlated with the content of this insoluble copper-protein. This would imply that copper- and zinc-thioneins occur as separate species, and thus would be contrary to current concepts that both cations are present, though in different ratios, in all forms of (copper, zinc)-thioneins (67,68). Whilst this may be true when the Cu:Zn ratio is high, it has been shown that crude preparations of (copper, zinc)-thionein (atomic ratio Cu:Zn = 1:1) from 1-3 day old pig liver, yield zinc-thionein as a single molecular species on preparative electrophoresis (63). No evidence has been obtained, however, that the hepatic content of mitochondrocuprein in newborn pigs is related to the tissue content of Zn^{2+} (63). Such a relationship might be expected if Zn^{2+} either prevents the polymerization of copper-thionein to mitochondrocuprein, or plays a role in the metabolism and elimination of this insolutle protein from the liver of the newborn.

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Validation Attempts of a Generic Approach for Regulating Air Toxics

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The validity of deriving ambient air quality standards or levels via threshold level values (TLVs) is assessed via two methodologies: (1) using current U. S. standards for ambient air standards and occupational standards where the data base is very robust and (2) using Soviet occupational and community air standards where the standards are based on experimentally derived toxicological endpoints. The analysis indicates that the TLV-derived approach using TLV/420 and the appropriate averaging time is in wide disagreement with both validating methodologies.

INTRODUCTION

Many states have initiated an attempt to develop "air toxics" regulations in the absence of a nationwide program on the federal level. Given the recognition that low concentrations of dozens of agents exist in ambient air, many states are opting for generic approaches to deriving acceptable air quality levels. While there are a number of variations, the basic pattern is often the same. This embodies the delineation of an ambient air quality standard (AAL) via a conversion of the industrial threshold level values (TLV) as derived by the American Conference of Governmental Industrial Hygienists (ACGIH). Since the TLV is based on predicting the health of occupationally exposed persons it usually assumes that exposures are confined to a 40-hr work week (i.e., 8 hr per day, 5 days per week) over the Years 18 through 65. Since ambient exposures entail 168 hr exposure each week (i.e., 24 hr per day, 7 days per week) over an entire lifetime (i.e., conception to death), various proposed modifications of the TLV have been proposed in order to make it more relevant to the ambient condition.

That an occupational health standard should be applied for deriving ambient air standards is highly controversial and not uniformly accepted. Nevertheless, it appears that many state regulatory offices have adopted what is widely considered a "pragmatic" approach. Since over 500 TLVs exist and have gone through a form of peer-review process and since the cost of doing each agent separately would be enormous, they have opted for some type of generic TLV-derived ambient standard regardless of the toxicological "correctness" of using TLVs for this purpose.

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In practical terms what frequently occurs is that the proposed ambient standard is some fraction of the TLV. For example, it is common for TLVs to be divided by 42 or 420 (TLV/42 or TLV/420), based on dividing the 40 hr per week exposure by 168, which yields 1/4.2, and then applying either a 10 or 100 safety factor. Other modifications may exist if one also wanted to amortize life span versus working years or respiration rate of children versus adults. The present paper is designed to offer two independent attempts to evaluate the validity of the generic approach using a TLV conversion factor for deriving AALs.

METHODOLOGY 1

The first attempt in considering whether dividing TLVs by 420 or some other value is valid is to assess what would be the ratio for agents where there is an enormous reservoir of toxicological and/or epidemiological data existing for both occupational and environmental (i.e., community) exposures. Take for example, SO_2, O_3, NO_2, CO, and Pb for which the United States has both national occupational and ambient air quality standards. If one were to use the TLV of each of these agents and divide by 420, how close would the value come to the ambient standard after adjusting for average periods? Would it underpredict or overpredict the value and by how much? As can be seen in Table 1, the methodology of dividing the TLV by 420 now is consistently more conservative or protective than that derived from actual data. For example, the ambient SO_2 standard for a 24-hr average of 365 mg/m^3 is about 1/13.6 of the occupational standard and not 1/420th of the value! Then, if one employs the current "known" pollutants to validate the proposed methodology, it would show that the TLV/420 approach is consistently more protective than current standards for which large data bases exist.

TABLE 1

COMPARISON OF TLVS AND AMBIENT AIR QUALITY STANDARDS IN THE UNITED STATES

	TLV	Ambient standard	Ambient TLV ratio
CO	50 ppm (~55 mg/m^3)	10 mg/m^3 (8-hr max)	$\frac{1}{5.5}^{a} / \frac{1}{14.2}^{b}$
O_3	0.1 ppm (~0.2 mg/m^3)	0.12 ppm (1-hr max)	$\frac{1}{2}^{c}$
SO_2	2 ppm (~5 mg/m^3)	365 $\mu g/m^3$ (24 hr)	$\frac{1}{13.6}$
NO_2	3 ppm (~5 mg/m^3)	0.100 mg/m^3 (annual)	$\frac{2}{5}^{d} / \frac{1}{60}^{e}$
Pb	0.15 mg/m^3	1.5 $\mu g/m^3$ (monthly)	$\frac{1}{50}^{d} / \frac{1}{100}^{f}$

Note. This table is an attempt to compare the U. S. ambient standards with the TLV counterpart.

[a] This represents a comparison of the 8-hr max with the TLV.

[b] This represents a comparison of a calculated 24-hr ave via the CRSTER model with the TLV.

[c] Stokinger (1972) estimate.

[d] This represents a comparison of a calculated 24-hr ave via the CRSTER model with the TLV.

[e] This represents a comparison of the annualized ambient standard with the TLV.

[f] This represents a comparison of the monthly ambient standard with the TLV.

METHODOLOGY 2

Another way to try to judge the validity of the proposed TLV-derived AAL methodology is to consider the relationship of the AAL to the TLV equivalent standard in countries where a large number of both standards are available and where the data are based on toxicologically derived endpoints for both types of standards and not on a TLV-derived methodology. The country with the most available standards for comparison is the Soviet Union.

The Soviet approach to setting acceptable exposure limits for occupational and ambient air pollutants has been written about in some depth in U. S. toxicological journals by both Soviet and American scientists [see Calabrese (1978) for a review]. The approaches used for standard setting by both countries are generally similar when it comes to viewing the AAL in relationship to TLV [or maximum acceptable concentration (MAC) as the Soviets call them]. Both countries recognize that the workplace

TABLE 2

CASES WHERE THE AMBIENT STANDARD IN THE SOVIET UNION IS GREATER THAN 1/420th OF THE OCCUPATIONAL HEALTH STANDARD

	Fraction of the occupational health standard
1. Epichlorohydrin	1/5.0
2. CCl_4	1/9.75
3. Sulfuric acid	1/10.00
4. Phthalic anhydride	1/10.00
5. Lead	1/14.2
6. Carbon monoxide	1/18.7
7. Benzene	1/22.5
8. Manganese	1/30
9. Hydrogen cyanide	1/33
10. Chlorine	1/33
11. Mercury, metallic	1/33.3
12. Ethylene oxide	1/36.0
13. NO_2	1/42
14. Trichloroethylene	1/48.1
15. HCl	1/49.0
16. Acetone	1/54
17. Pyridine	1/56.2
18. Acrolein	1/60
19. Hydrogen fluoride	1/80
20. Toluene	1/81.2
21. Acetic acid	1/83
22. Formaldehyde	1/100
23. Arsenic	1/100
24. Methyl alcohol	1/104
25. Ammonia	1/108
26. SO_2	1/156
27. Furfural	1/200
28. Ethanol	1/201
29. Xylene	1/261
30. Nitrobenzene	1/375

TABLE 3

CASES WHERE THE AMBIENT STANDARD IN THE SOVIET UNION IS LESS THAN 1/420th OF THE OCCUPATIONAL HEALTH STANDARD

	Fraction of the occupational health standard
31. Phenol	1/494
32. Chlorobenzene	1/506
33. Tetrahydrofuran	1/516.2
34. Propyl alcohol	1/666
35. Aniline	1/1,013
36. Amyl acetate	1/1,050
37. Hydrogen sulfide	1/1,313
38. Methyl acetate	1/1,534
39. CS_2	1/1,800
40. Ethyl acetate	1/1,925
41. Butyl acetate	1/2,130
42. Naphthalene	1/6,666
43. Styrene	1/16,800

standard is designed to protect a worker from an 8-hr exposure for 5 days per week for 50 weeks per year between the normal work years of 18 to 65 years of age. However, an AAL must protect the general public including the young and aged, persons at enhanced risk due to preexisting diseases such as respiratory illness, and others. Consequently, the AAL will be a much lower number than the TLV (or MAC). The principal difference between the two countries relates to what is termed an "adverse health effect." The Soviets consider any physiological/biochemical deviation from normal as unacceptable. However, the United States may view certain initial alterations (e.g., enzyme induction) as indications of an adaptive response. The net result is that Soviet standards for both MACs and AALs are often considerably lower than their U. S. counterpart standards (Izmerov, 1973).[1]

Regardless of these differences, the ratio of AAL to TLV should be comparable between the two countries. This is one reason why it is deemed of great interest to see to what extent the Soviet AAL is a mathematical relationship of their MAC. In addition, the Soviet AALs are actually based on experimental studies usually with animal models focusing on the most sensitive biological parameters such as olfactory response, enzyme alterations, etc., along with 0.3-fold safety factor down from the no effect level.

In the present evaluation, 114 Soviet AALs were obtained. From this total, forty-three 24-hour average AALs with corresponding MACs [i.e., 8-hr maximum (not time weighted)] values (Tables 2 and 3) were compared. The remaining 71 AALs were not compared because of a lack of available MAC, no 24-hr average value, etc. The results indicated that about 70% (30 of 43) of the AALs had values that were considerably higher than the 1/420 TLV methodology. Thirteen of the 43 agents had values much lower than the 1/420 TLV proposed methodology. The total variation was enormous, being from 1/5 to 1/16,800 of the MAC! The toxicological basis for such differences is known from the U. S. literature for but a few of these agents. Nevertheless, it is known that these values are experimentally derived and not just a numerically con-

[1] It should be noted that we are not discussing compliance with the proposed standards.

jectured value. This being the case, it calls into question the generic approach which treats all agents in a similar manner. If the Soviet approach were a good model, it would suggest that the TLV/420 methodology would often have much "unneeded" safety built in, while at other times not enough.

DISCUSSION

The two independent attempts to validate a currently in vogue methodology for deriving AALs from TLVs indicate potentially serious problems. The U. S. data, based on our current ambient air standards, suggest that the TLV/420 methodology may grossly overpredict risk while the Soviet data imply that this methodology may grossly under and/or overpredict risk based on the agent. While any generic approach would be expected to be somewhat off the mark and on the conservative side, the magnitude of the potential inconsistencies is so large as to seriously question the validity of this approach. Clearly, further attempts to assess the validity of this and other generic approaches to establishing public health-based AALs are needed before such standards become adopted in numerous states.

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INFLUENCE OF TOTAL DOSE AND DOSE RATE IN CARCINOGENICITY STUDIES

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One element of the ED_{01} Study contained a group of animals that were dosed with 2-acetylaminofluorene for 9, 12, 15, 18, or 24 mo and then sacrificed at 18 or 24 mo. This provided data to compare the relative effects on carcinogenicity of dose rate versus total dose. The prevalence of liver and bladder tumors were used as the comparison. Animals receiving similar total doses but over a different length of time (different dose rates) were compared at the 18- and 24-mo sacrifices. When the total doses were similar, the higher dose rates for shorter time periods induced a higher prevalence of tumors. Results were more consistent for bladder tumors than for liver tumors, although the same trends were noted for both endpoints. Those groups dosed at higher rates but for fewer months had a generally higher prevalence than those receiving similar total doses but at lower rates for more months. This data from the ED_{01} Study illustrates the importance of experimental design, dosing regime, length of study time, and age of the animals at time of dosing in respect of calculation of risk.

INTRODUCTION

Chronic toxicology studies for the determination of carcinogenicity are usually conducted by administering the agent to the animals in their feed or water at calculated concentrations for specified lengths of time. These studies often include sacrifice intervals in which part of the animals are removed from the study and an examination made at some interim point in the lifetimes of the animals. These studies are generally terminated around the average lifespan of the animal species on study. At the terminal sacrifice, the animals are killed and microscopic histopathological examinations conducted. Estimates of risk are calculated on positive studies based on the concentration of the test agent in the feed or water of the test animal. Almost always, studies are conducted in which dosages are administered ad libitum and continue until the time when the animal is removed from the study. One element of the ED_{01} Study (Littlefield et al., 1980), a study performed to determine the possibility of determination of the effective dose of a carcinogen at the 1% level, contains groups of animals that were dosed for specific periods of time, after which the carcinogen was removed

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removed from the feed and the animal was subsequently held for additional time periods prior to sacrificing. Since concentrations of the carcinogen were determined analytically in each batch of feed and feed consumption was measured, the data are available to study the effects of dose rate, or the dose schedule, using several different groups of animals having different dosing periods, but were sacrificed after the same lifespan. The purpose of this paper is to examine the influence that the dosing regime (i.e., dose rate and total dose) may have on the relative results of a carcinogenicity study.

METHODS

The complete methods, results, and analysis of this study are found in Littlefield et al. (1980). The experimental design with respect to numbers of animals sacrificed at each dose level is shown in Table 1. For the purposes of this paper, serial treatment groups are used. BALB/c female mice were dosed at 0, 60, 75, 100, and 150 ppm, in the feed, commencing as weanlings, for 9, 12, 15, 18, or 24 mo, then sacrificed at either 18 or 24 mo. The carcinogen in the feed was 2-acetylaminofluorene (2-AAF). The average total dose in milligrams 2-AAF per mouse was determined using each group of mice that was sacrificed and was calculated from the food consumption data recorded on each cage weekly. The total dose used in the results was based on the average dose per mouse per cage, since some animals in each group died prior to sacrifice. The target concentration was used in the calculation and the total dose was calculated by multiplying the concentration in ppm by the food consumption. The NCTR mouse feeder (Hunziker, 1975) was used. This feeder has been shown to prevent spillage at a rate consistently less than 1%.

Models for estimating liver and bladder tumor prevalence rates are, respectively,

TABLE 1. Number of Animals Sacrificed at Each Dose and Time Interval

	Time of sacrifice (mo)							
	18	24	18	24	18	24	18	24
	Time on dose (mo)							
Dose (ppm)	9	9	12	12	15	15	18	24
150	63	33	63	29	65	28	121	130
100	64	35	65	33	64	35	131	160
75	128	66	132	74	130	86	267	311
60	184	108	190	118	196	114	269	415
0							400	384

$$\ln(P_L + 0.5) = 2.1236 + 0.004175r + 0.00330d$$
$$P_L = -0.5 + \exp(2.1236 + 0.004175r + 0.003330d)$$
$$\ln(P_B + 0.5) = -1.8428 + 0.00014331r^2 + 0.011020d$$
$$P_B = -0.5 + \exp(-1.8428 + 0.00014331r^2 + 0.011020d)$$

where P_L is the estimated percent of animals with liver tumors (prevalence) at 24 mo, P_B is the estimated percent of animals with bladder tumors (prevalence) at 24 mo, dose rate r is given as ppm 2-AAF, and total dose d is the average milligrams per mouse of 2-AAF. The constants in the exponents of the models were obtained by the method of least squares.

RESULTS

The average total dose received by the respective dose groups of animals and the prevalence of liver and bladder tumors are shown in Table 2.

There are several comparisons that can be made from Table 2, in which animals received a similar total dose but at different dose rates. For instance, mice that received 160 mg 2-AAF at 75 ppm over 24 mo can be compared to another group that received 153 mg 2-AAF at 150 ppm for 12 mo. Both groups were sacrificed at 24 mo. The prevalence of both liver and bladder tumors were higher in the group receiving the higher dose rate for 12 mo. Mice dosed at 60 ppm (128 mg 2-AAF) for 24 mo had the same liver tumor prevalence but a slightly lower bladder tumor prevalence than a group dosed at 100 ppm (133 mg 2-AAF) for 12 mo. Two other groups (97 mg 2-AAF over 15 mo at 75 ppm versus 100 mg 2-AAF over 12 mo at 100 ppm) showed essentially the same results. However, 2 other groupings (78, 77, and 76 mg 2-AAF over a dosing period of 15, 12, and 9 mo at 60, 75, and 100 ppm, respectively, and 61 and 57 mg 2-AAF over 12 and 9 mo at 60 and 75 ppm, respectively) showed somewhat inconsistent results in the liver tumors, while no bladder tumors appeared in these groups. All of the groups already mentioned were sacrificed at 24 mo.

Comparisons that were made in the animals sacrificed at 18 mo showed a lower prevalence in the liver tumors, since this lesion was a late-developing tumor. However, the results in bladder tumors showed some consistent trends. The most prominent example was the two groups having a total dose of 148 mg 2-AAF (100 ppm for 18 mo) and 149 mg 2-AAF (150 ppm for 12 mo). The prevalence was 4% in the group having the 100 ppm dose rate, and 22% in the group having a dose rate of 150 ppm. Two other groups (113 and 114 mg 2-AAF for 18 and 9 mo at 75 and 150 ppm) exhibited a prevalence of 1 and 6%, respectively, while 3 other groups (74, 75, and 71 mg 2-AAF over a dosing period of 15, 12, and 9 mo at 60, 75, and 100 ppm, respectively) showed bladder tumors appearing only in the group dosed at 100 ppm, which was the highest dose rate. This was also noted in groups receiving 91, 94, and 97 mg 2-AAF, and another grouping receiving 60 and

TABLE 2. Total Dose (mg 2-AAF/Mouse) and Subsequent Prevalence of Liver Tumor and Bladder Tumor for BALB/c Mice

		Month of sacrifice							
		18	24	18	24	18	24	18	24
		Months dosed							
Dose (ppm)	Parameter	9	9	12	12	15	15	18	24
150	Total dose	114	116	149	153	186	195	224	316
	Liver tumor, %	6	27	3	31	6	21	6	43
	Bladder tumor, %	6	18	22	24	34	39	51	77
100	Total dose	71	76	97	100	127	133	148	211
	Liver tumor, %	2	14	0	15	2	17	5	30
	Bladder tumor, %	2	0	2	3	0	3	4	16
75	Total dose	56	57	75	77	94	97	113	160
	Liver tumor, %	2	15	5	19	4	16	2	20
	Bladder tumor, %	2	0	0	0	0	0	1	1
60	Total dose	45	45	60	61	74	78	91	128
	Liver tumor, %	1	12	1	9	2	13	3	17
	Bladder tumor, %	0	1	0	0	0	0	1	1

56 mg of 2-AAF; i.e., the higher prevalence was noted in these groups in which the higher dose rate was given over a shorter time period.

The general concensus of these comparisons shows the liver tumor data as not consistent over all ranges, but does exhibit a trend toward a higher prevalence associated with the higher dose rates. The bladder tumor data were more consistent in this respect. When the total doses were similar, the higher dose rates for shorter time periods induced a higher prevalence of bladder tumors.

The total dose was calculated for each treatment group. The respec-

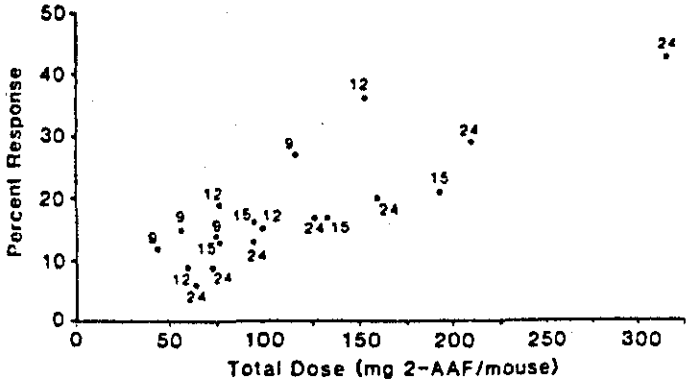

FIGURE 1. Relationship of total dose, dose rate, and incidence of hepatocellular carcinoma in 24-mo-old mice. Number indicates duration of dose (months).

FIGURE 2.
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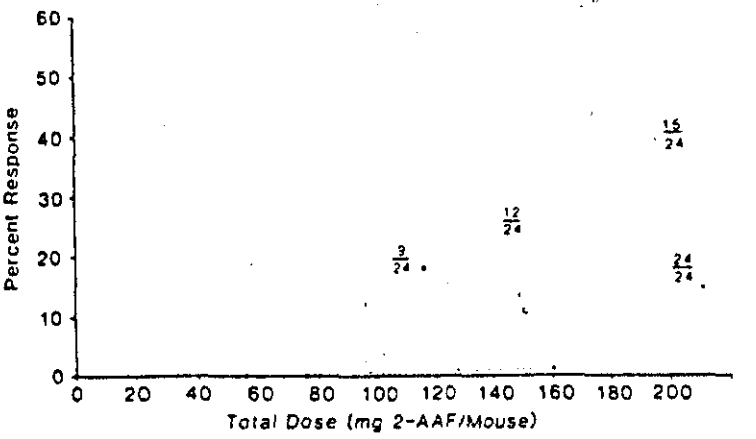

FIGURE 2. Relation of total dose, dose rate, and incidence of bladder tumors in mice sacrificed at 24 mo. Number indicates (months dosed)/(months at sacrifice).

tive prevalence of hepatocellular carcinoma for each of these treatment groups was determined and the resulting data are shown in Fig. 1. The total dose (mg 2-AAF/mouse) is compared against the prevalence at the 24-mo sacrifice. Those groups dosed at higher rates, but for fewer months, have a generally higher prevalence than those receiving similar total doses, but at lower rates for more months. Therefore, the dose rate appears to influence the prevalence of hepatocellular carcinomas irrespective of the total dose. For example, mice receiving a total dose of 153 mg 2-AAF over a period of 12 mo had a prevalence of 31% hepatocellular carcinomas, as compared to only 20% in mice receiving a total dose of 160 mg 2-AAF over a 24-mo period.

For bladder tumors, the same effect is noted in Fig. 2. A dose-rate effect is very evident, in that the animals receiving the same dose but over a shorter time interval had the higher prevalence of bladder tumors.

DISCUSSION

The data presented indicate that under the conditions of this study, both dose rate and length of exposure (total dose) influence the carcinogenic response. Animals dosed for 9 or 12 mo and sacrificed at 24 mo had a much higher prevalence of both liver and bladder tumors than a group given a similar total dose for 18 or 24 mo. This has important implications related to choices of experimental designs, especially in quantitative carcinogenesis studies designed for calculation of risk. For instance, 160 mg 2-AAF administered over 24 mo resulted in a 20% prevalence of liver tumors, whereas approximately the same total dose of 153 mg given for 12 mo (i.e., at twice the dose rate), with the sacrifice at 24 mo, resulted in a prevalence of 31% liver tumors, a 55% increase in tumor prevalence. Higher dose rates for shorter periods of time appear to be more effective for producing positive

results than lower dose rates given over longer periods of time. This also supports the concept that smaller numbers of animals at higher dose rates could be used to obtain significant results. Also, in view of the high cost of conducting toxicology studies, costs could be reduced by dosing the animals for the first 9 to 12 mo, then merely holding them until sacrifice at 24 mo. This would eliminate the cost of diet preparation and subsequent chemical analysis and diet monitoring for 12-15 mo. However, this reduces the chance of detecting tumors compared to using the higher dose rate for 24 mo. Also, dose rates are limited to the amount that animals can tolerate.

The amount of data in the literature in which total dose can be compared with dose rate is sparse. One study, conducted by McCornick et al. (1981), gave a total dose by intragastric instillation of 30, 20, or 15 mg *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in 20, 10, or 5 weekly fractions. These data showed that the doses given in the 20 weekly fractions were more effective in producing urinary bladder cancer than those given in the 5 weekly fractions. Although it is not clear whether the 5 weekly fractions were given in the first 5 wk or evenly spread throughout the 6-mo study period, these higher dose rates did not produce the same results as the present study. Although the reason is not clear, it could be due to a chance for recovery with the five fractions.

Druckrey (1967) stated that the total dose needed to produce cancer with small daily doses over a long period is not greater, but significantly smaller. Carcinogenic action goes considerably beyond a pure "summation action" and increases with time. Druckrey theorized that time is inversely proportional to dose. Druckrey showed that the tumor rate decreases when the total dose of diethylnitrosamine is spread at lower doses over a longer time. In the study reported here, all animals were sacrificed at the same time, therefore, time is not a factor.

Another factor that possibly had an influence in this study is that in many instances young animals are more susceptible to exposures of carcinogens than older animals. Therefore, since the higher dose rates were administered to the animals during the first 9 or 12 mo of their lifespan, they might exhibit the higher prevalences.

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The inhalative toxicity of different cadmium compounds in rats*

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Abstract. In a long-term inhalation study, male and female Wistar rats were continuously exposed to submicron aerosols of CdO, $CdCl_2$, $CdSO_4$, CdS and a CdO/ZnO combination. For chronic exposures it was shown that at aerosol levels equal to and above 90 µg/m³ Cd, even the less soluble cadmium compounds (CdO and CdS) were toxic and lethal, especially to male rats. No mortality was seen in the group exposed to the ZnO/CdO combination. Our study suggests that inhalative toxicity of cadmium compounds may be related to lung retention of bioavailable cadmium. In a short-term inhalation study we found that the lung retention of cadmium was two times higher after exposure to CdO than to $CdCl_2$. The lung and body burden of cadmium differed by a factor of ten between CdO and CdS. The reasons behind these results are not yet fully understood.

Key words: cadmium compounds – inhalation – retention – toxicity – Wistar rats

Introduction

It has been shown from long-term inhalation studies that cadmium chloride induced primary lung tumors in Wistar rats, and that the incidence of lung tumor was strongly dependent on the cadmium aerosol concentration [Takenaka et al. 1983, Oldiges et al. 1983, Oldiges et al. 1984]. It was therefore logical to examine whether other less soluble cadmium compounds to which human beings are more frequently exposed have the same carcinogenic potency as cadmium chloride.

Material and methods

Long-term inhalation study

In a long-term inhalation study rats were exposed to cadmium aerosols consisting of cadmium chloride ($CdCl_2$), cadmium oxide (CdO) as dusts and fumes, cadmium sulfate ($CdSO_4$), and cadmium sulfide (CdS). Another group of rats was exposed simultaneously to dusts consisting of zinc oxide (ZnO) and cadmium oxide. The rats were exposed in 2251 horizontal flow inhalation chambers. Two wire mesh cages were placed in each chamber and each cage contained 10 rats.

The aerosols were generated by several different systems described previously [Hochrainer 1983]. The aerosol flow-rate was 80 l/min. The particles of the cadmium aerosols were in the submicron size range and had average mass medium diameters ranging from 0.2 to 0.5 µm. The particle size distributions and the cadmium aerosol concentrations were measured as described elsewhere [Oberdörster et al. 1979].

Five week-old inbred Wistar rats (TNO-W-75, SPF) were used. For each aerosol concentration and for each cadmium compound there were 20 female and 20 male rats, purchased from F. Winkelmann GmbH, Borken, FRG. 40 animals breathing filtered air were kept as controls (Table 1). The inhalation laboratory is an air-conditioned room with a 12 hrs day/night cycle. The animals received drinking water ad libitum. To keep the cadmium uptake from food as low as possible the animals were fed with a Ssniff pellet diet between 4 p.m. and 8 a.m. The rats were continuously exposed for 22 hrs a day, 7 days a week. As in the previously reported experiment the exposure time was to be 18 months and the studies were to be terminated in the 31st month, that being the mean survival lifespan of the strain.

Short-term inhalation study

To obtain more information about the lung deposition and retention of the different cadmium compounds, short-term inhalation studies with 100 µg/m³ Cd as cadmium chloride, 100 µg/m³ Cd as cadmium oxide dust and 1 mg/m³ Cd as cadmium sulfide were performed.

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Table 1 Inhalative toxicity of different cadmium compounds in rats

Group No.			nominal aerosol concentration ($\mu g/metal/m^3$)	measured concentration ($\mu g/metal/m^3$)	duration of the study (days)	exposure (days)	mortality incidence
1.)	controls	♂♂	-	-	343	-	1/20
2.)	controls	♀♀	-	-	343	-	0/20
3.)	$CdCl_2$	♂♂	30	29 ± 5	255	255	0/20
4.)	$CdCl_2$	♀♀	30	29 ± 4	255	255	0/20
5.)	$CdCl_2$	♂♂	90	91 ± 14	441	180[a]	0/20
6.)	$CdCl_2$	♀♀	90	92 ± 13	441	180[a]	1/20
7.)	CdO dust	♂♂	30	30 ± 4	343	343	0/20
8.)	CdO dust	♀♀	30	26 ± 4	343	343	0/20
9.)	CdO dust	♂♂	90	90 ± 9	343	218[b]	6/20
10.)	CdO dust	♀♀	90	81 ± 8	343	324[b]	6/20
11.)	CdO/ZnO dusts	♂♂	90/900	102 ± 20/945 ± 106	374	374	0/20
12.)	CdO/ZnO dusts	♀♀	90/900	103 ± 20/949 ± 136	374	374	0/20
13.)	$CdSO_4$	♂♂	90	95 ± 14	455	413[b]	6/20
14.)	$CdSO_4$	♀♀	90	92 ± 13	455	455	1/20
15.)	CdS	♂♂	90	91 ± 17	409	409	1/20
16.)	CdS	♀♀	90	92 ± 20	402	402	0/20
17.)	CdS	♂♂	270	254 ± 78	409	409	3/20
18.)	CdS	♀♀	270	263 ± 75	409	409	2/20
19.)	CdS	♂♂	810	843 ± 211	409	208	6/20
20.)	CdS	♀♀	810	841 ± 209	402	298[b]	7/20
21.)	CdS	♂♂	2430	2270 ± 545	112	112[b]	5/24
22.)	CdS	♀♀	2430	2247 ± 543	105	105[b]	4/24
23.)	CdO-fume (n = 40)	♂♂	10	10 ± 3	243	243	0/40
24.)	CdO-fume (n = 40)	♂♂	30	31 ± 4	243	249	0/40

a) The planned inhalation time was 180 days

b) exposure interrupted due to more than 25% mortality

A higher concentration of cadmium sulfide was chosen because of the very low solubitity of this compound. Groups of six five-week-old male rats were continously exposed to the cadmium aerosols for one month under the same conditions as described above. After exposure each parallel group breathed filtered air for a further two month period before being sacrificed (using urethane anesthesia).

Results

Long-term inhalation study

Since there were no results in the literature regarding the long-term inhalative toxicity of cadmium compounds other than our own with cadmium chloride, we chose higher cadmium aerosol concentration for cadmium sulfate, oxide and sulfide, because of their lower solubilities. However, in some cases the chosen aerosol concentrations were too toxic and those exposures were stopped. For these groups mortality occurred within a few weeks, suggesting that there is a critical lethal concentration. This toxicity (Table 1) was not apparent earlier, either through the regular checks on weight gain, food and water consumption, or by hematological examinations. Gross necropsy of the dead animals revealed increased lung weights and enlarged thoracal lymph-nodes. Elevated liver weights were found only in the rats exposed to the highest cadmium sulfide aerosol concentration (2.4 mg/m^3 Cd) (Table 1). No further mortality occurred after termination of cadmium exposure in those groups which had shown increased mortality incidence. The weight gains of the surviving rats were similar to those of the controls. The selected cadmium aerosol concentrations of the different cadmium compounds and the available results (Table 1) show that at 90 $\mu g/m^3$ Cd or higher, cadmium was toxic as an oxide, a sulfate or a sulfide, especially to the male rats. There was no lethality observed in the cadmium zinc combination group. Cadmium sulfide proved to be toxic with a clear-cut aerosol concentration dependency.

In an earlier experiment we showed that cadmium chloride aerosols had a lung clearance half-life of about 60 days [Oberdörster et al. 1980]. The results of this study showed that this must be true for cadmium oxide and sul-

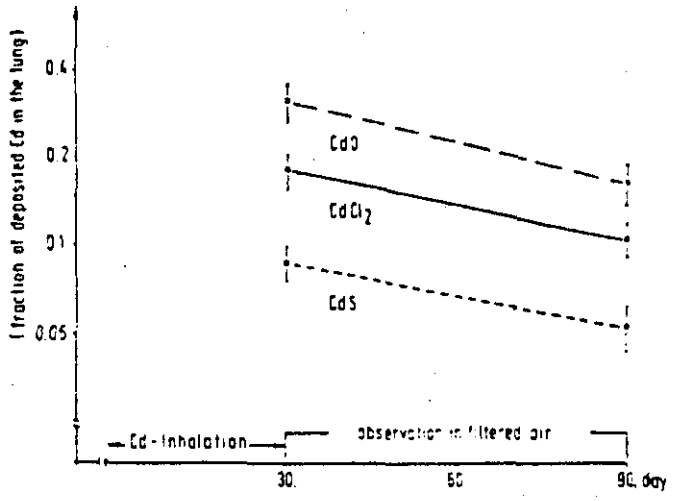

Fig. 1. Cadmium retention in the lung of male Wistar rats (n = 6 per group) after continuous exposure to submicron cadmium aerosols (0.1 mg/m³ Cd as $CdCl_2$ and CdO, 1 mg/m³ Cd as CdS). Numbers on ordinate represent relative lung burden, calculated from Stahl's formula with a 30% deposition rate in the alveolar region.

fide aerosols as well (Figure 1). This figure shows that continuous exposure to submicron cadmium aerosol as CdO resulted in a cadmium retention in the rats' lungs two times higher than for treatment with a cadmium chloride aerosol of the same concentration and particle size. Exposure to the less soluble CdS aerosol also resulted in a lower Cd retention in the lungs. In addition to the results for cadmium retention in the lungs, Figure 2 gives the cadmium distribution found in the kidneys and livers. It is evident that cadmium exposure as cadmium sulfide, although ten

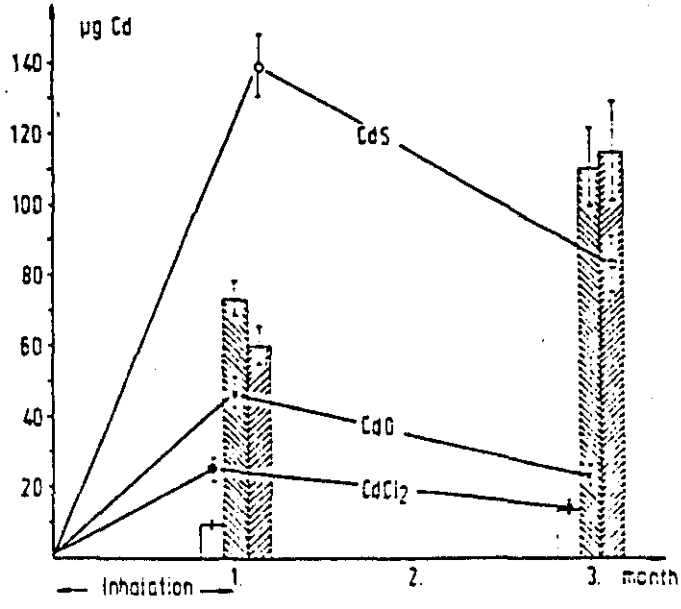

Fig. 2. Cadmium retention in the lungs (lines) and Cd body burden in the kidneys and livers (column 1: 0.1 mg/m³ Cd as $CdCl_2$, column 2: 0.1 mg/m³ Cd as CdO, column 3: 1 mg/m³ Cd as CdS) after a one month inhalation and a subsequent two month observation period. Means ± S.D. of 6 male rats each group.

times higher, resulted in the same cadmium body burden as for the exposure to the CdO aerosol. This was observed at the end of the 30-day inhalation period and at the end of the subsequent observation period. These results support the available results of the long-term inhalation study that in addition to the soluble cadmium chloride aerosols, the submicron Cd-aerosols of lower solubilities are just as bioavailable and just as toxic to experimental animals.

Discussion

Several authors suggested that in some occupations cadmium aerosols may be a carcinogenic risk [Lemen et al. 1976, Kjellstrom et al. 1979]. Recently it was demonstrated that long-term exposure of experimental rats to submicron aerosols of cadmium chloride induced primary lung tumors at even low exposure level [Takenaka et al. 1983]. But presently there is no clear knowledge about the kinetics and inhalative potencies of other cadmium compounds, especially the less soluble ones. Thus a long-term inhalation study was designed to describe the carcinognic risk from CdO dusts and fumes, $CdSO_4$, CdS and a CdO/ZnO combination. But in relation to $CdSO_4$ as well as the water insoluble compounds CdO and CdS, it was shown that aerosol levels equal to or higher than 90 µg/m³ were toxic and lethal to male Wistar rats. Epidemiological data of Princi [1947] and Teculescu and Stanescu [1970] did not reveal any symptoms of toxcicity after inhalation of CdO and CdS dusts and fumes at even higher exposure levels. Our findings concerning toxcicity of these Cd compounds have been confirmed by short-term kinetic studies. Hadly et al. [1980] found that CdO instilled intratracheally rapidly translocated to the livers of rats. The results of Cd retention in this study confirm that CdO was slightly more available to the lungs than $CdCl_2$, while CdS retention was lower. The reason for the observed differences in behavior of the various cadmium compounds should be examined in future studies.

Acknowledgements

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Cadmium oxide

~~CdO~~ Toxicity: Macromolecular Binding of Cadmium, Zinc, and Copper in the Fibrotic Rat Lung

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ABSTRACT

Rats were exposed to CdO aerosols for 9 to 13 months at levels of about 300 μg Cd^{2+}/m^3. Cadmium-, zinc-, and copper-containing protein fractions were obtained from the lungs and kidneys of these animals by dialysis and Sephadex gel chromatography. The proteins of the lung and kidney that bind these metals do not appear to be identical but have properties in common. For the first 9 months of exposure, the majority of cadmium in the lung is bound to a low-molecular-weight component resembling metallothionein, whereas the kidneys of these animals possess an additional 30% of the available cadmium bound to several polypeptides with molecular weights of between 1000 and 4500. After 13 months of exposure, no metallothionein-like fraction was observed in the lung but was observed in the kidney. Instead, 46% of the available lung cadmium was contained in the ultrafiltrate bound to lower-molecular-weight components.

Although the absorption, distribution, metabolism, toxicity, and excretion of cadmium has been the subject of extensive study,[1,2] less research has been concerned with respiratory deposition and subsequent metabolism of cadmium-containing dusts, aerosols, or fumes.[3-7] However, the relationship between elevated levels of cadmium in the lung and pulmonary emphysema or bronchitis has been noted for years.[8-10]

The metabolic fate of cadmium-containing compounds administered by other routes of entry[11-23] has been followed. From such investigations it has been established that, once absorbed, cadmium rapidly appears in the plasma and then shifts to the red blood cells where it associates with hemoglobin. In rats or mice, accumulation in the liver commences almost immediately,[13-23] where the largest concentration binds to a low-molecular-weight protein, metallothionein, after an induction lag of several hours.[17,24-39] During the first 24 hr following an injected dose and after repeated injections, cadmium has also been found associated with high-molecular-weight proteins in liver and kid-

ney[17,19,26-28] which to date have been little characterized structurally. The high-molecular-weight protein–cadmium association in experiments with repeated doses has been postulated as representing excess cadmium spillage from the sequestering metallothionein.[26] After the first day, cadmium is found in the kidney as well as in the liver, again principally bound to metallothionein. These two organs accumulate the bulk of the metal administered by injection or the oral route with very little (about 1%) being distributed to the lungs.[1,12,25] In one chronic inhalation study, pulmonary absorption was calculated as representing 30% of that inhaled, and only 10% of the total cadmium recovered from the lung, liver, and kidney remained in the lung.[1,6]

This work has been undertaken to evaluate the response of the lung to cadmium oxide aerosols since studies relating exposure to cadmium with lung disease have not been followed by more detailed work directed toward elucidating the molecular mechanisms of toxicity. Cadmium was measured after varying exposure periods and located with respect to its subcellular distribution and protein association. Its distribution among the different proteins of the lung was compared with that occurring simultaneously in the kidney. It was expected that inhaled cadmium would be bound to some proteins bearing structural similarities to each other as well as to those isolated from animals given cadmium by other routes. Since at least the protein metallothionein, whether extracted from the liver or kidney in a variety of hosts[25-27,31], has been demonstrated to be remarkably similar in amino acid composition and metal binding, this assumption seemed reasonable. This paper presents data identifying rat lung and kidney cadmium-binding proteins in terms of their molecular weights and metal compositions at moderately advanced stages of lung fibrosis as measured by light and electron microscopy.

MATERIALS AND METHODS

Animals

Each experimental group was composed of 15 control and 15 exposed white Sprague–Dawley rats (Laboratory Services) that were 3 months old at the commencement of the inhalation experiments. Body weights commenced at a mean of 330 ± 10 g (±SD) and were 515 ± 50 g (±SD) at the time of death. The animals were maintained in stainless-steel cages in air-conditioned quarters on standard laboratory chow (Purina) with tap water *ad libitum*.

Inhalation Chambers and Aerosol Generation

The animal exposure chambers had an internal volume of 12 ft^3 with a conical top feed and bottom exit. The aerosols were generated by passing nebulized cadmium acetate through a 600°C oxidation furnace. The effluent airstream was cooled by a series of condensers so that the final temperature entering the chamber ranged from 35° to 40°C (Ref. 31). The effluent from the

chamber was passed through an absolute filter before venting. During the exposure periods, aerosol particles in a known volume of air from the exposure chamber were collected on Millipore filters for metal analyses by atomic-absorption spectrophotometry. The size distribution of the aerosol in the chamber was measured with a seven-stage Andersen impactor equipped with a 47-mm Type AA, 0.8-μm Millipore backup filter[32] (mass median aerodynamic diameter = 0.15 μm, σg = 2.53). Atomic-absorption spectrophotometry was used to analyze all stages for metals. The chemical composition of the particles was verified by X-ray analysis and electron spectroscopy for chemical analysis (ESCA). In solution, CdO is insoluble except in the presence of acids or ammonium salts.[33]

Inhalation Experiments

The inhalation procedures used were previously established in these laboratories.[31,34,35] Groups of 15 animals each were housed within the chambers in compartmentalized stainless-steel racks for the duration of the exposure period, after which they were returned to their regular quarters. Exposure periods lasted 7 to 8 hr per day, 5 days per week, for a total duration of 9 to 13 months. The mean chamber concentration for each exposure period was 347.5 ± 73 (SD) μg Cd^{2+}/m^3 and 282.1 ± 95.2 (SD) μg Cd^{2+}/m^3, respectively. The same number of control rats for each experiment were maintained in a laminar air-flow apparatus for the duration of the experiment. On the basis of a respiratory clearance of 0.01026 m^3/hr times the number of hours in the chamber, these two groups have inhaled 4604.8 and 5487.7 μg Cd^{2+}/rat, respectively.[35] At pulmonary compartment deposition rates of 0.2 to 0.3 of that inhaled, the calculated amount of Cd^{2+} deposited was 1151.2 μg for the 9-month exposure and 1371.9 μg for the 13-month exposure. The cadmium recovered from the lung was considered a direct reflection of that absorbed after deposition, whereas kidney cadmium was assumed to also include the fraction absorbed after ingestion. The equilibrium concentration for the lung was about 130 μg Cd^{2+} per animal.[35] After exposure of 13 months, the kidney concentration had not reached an equilibrium value.

Reagents and Glassware

All chemicals used for analyses were ultrapure or of reagent grade. All water used was triple distilled in a glass apparatus. All glassware was boiled in aqua regia, followed by rinsing in distilled water, soaked in 1% (w/v) ethylenediaminetetraacetic acid disodium salt (EDTA), and rinsed again 5 to 10 times.

Buffers [composed of 0.25*M* sucrose and 0.001*M* 2-amino-2-(hydroxymethyl)-1,3-propanediol (Tris), pH 7.4; 0.02*M* Tris, pH 8.6; and 0.001*M* Na_2CO_3, pH 7.4] were prepared on the day of use. Concentrated stock solutions of the metals and all other solutions were prepared as previously described.[34]

Metal Analyses

Analyses were performed on a Perkin–Elmer 403 atomic-absorption spectrophotometer equipped with a Boling triple slot burner and an air–acetylene flame. Sensitivity of the instrument for cadmium, zinc, and copper was 0.01 ppm at 1% absorption. The detection limit, under the experimental conditions, was 0.02 μg/ml for all three metals.

All supernatant samples were digested with 24% tetramethylammonium hydroxide in methanol before analyses. Digestion required 1 hr at 60°C in a shaking incubator at a 1:50 (w/v) ratio of sample to base. Reagent blanks and standard curves were analyzed concurrently. External standards were used.

Preparation and Fractionation of Tissue

With the use of a previously established technique,[35] anesthetized rats were opened and their lungs perfused through the heart with the sucrose–Tris buffer (pH 7.4) to remove the blood. The lungs were then washed 5 times with a 10-ml buffer via tracheal cannulation to remove alveolar macrophages, lung surfactant, and any remaining cadmium oxide particles,[36–38] after which they were stripped of the bronchi, rinsed, weighed, pressed, and homogenized (see "Results and Discussion"). Kidneys were rinsed, weighed, and transferred directly to the cold sucrose–Tris–HCl homogenization medium. The respective organs for each experiment were pooled before homogenization and fractionation. For some experiments the organs were frozen and stored at −20°C before homogenization.

The homogenization and fractionation procedure was an adaptation of standard methods.[7–37,39–42] For each preparation the organs from five animals were homogenized in 5 volumes of the above-mentioned sucrose–Tris–HCl buffer followed by centrifugation at 12,100 *g* for 30 min and 1000,000 *g* for 60 min to remove the subcellular components. The supernatants from the centrifugation were either lyophilized or subjected to ultrafiltration before further treatment. The final supernatant fractions were usually analyzed immediately for metals but could be stored at −20°C without alteration in their metal concentrations.

Ultrafiltration

Concentration to one-third of the original volume was performed under nitrogen at 50 psi at 4°C in a thin channel separator equipped with a UM-2 filter (molecular weight cutoff, 1000). The final ultrafiltrate (about 15 ml) was rinsed from the filter with 3 by 1 ml buffer and applied directly to the first column (Sephadex G-75).

Dialysis

Sodium carbonate buffer (0.001 *M*), pH 7.4, was used for dialysis at 4°C. The ratio of buffer to supernatant was maintained at 20 : 1. The buffer was changed

three times during a 27-hr period. The cellulose dialysis tubing (molecular weight cutoff, 3500) was pretreated to remove contaminating metal ions.[29,30] Larger pore tubing (molecular weight cutoff, 6000 to 8000) was used in a second series of experiments following the first series (see "Results and Discussion"). For the experimental group exposed to CdO aerosols for 13 months, the original protocol for dialysis was altered to include the use of the ultrafiltration apparatus to dialyze the supernatants. In this set, after centrifugation, the soluble extract was concentrated and the ultrafiltrate was dialyzed twice in succession within the same system with approximately 20 volumes of the buffer at 50 psi.

GEL FILTRATION EXPERIMENTS

Estimation of Molecular Weights

For the estimation of molecular weights of the metal-binding proteins, samples were chromatographed at 4°C on Sephadex G-200, G-100, G-75, and G-50 in columns equipped with flow adaptors for ascending and descending chromatography. The respective bed volumes were: 215 ml, 254 ml, 377 ml, and 44 ml. Tris–HCl buffers (0.02M, pH 8.6 and 7.6) were used at flow rates of 6 to 30 ml/hr depending on the gel, and fractions of 3 to 6 ml were collected. Reference samples (about 1% of the bed volume) were 0.2% in blue dextran and contained 0.2 to 4 mg/ml each of two of the relevant reference proteins. The seven reference proteins used were (1) thyroglobulin, (2) catalase, (3) aldolase, (4) ovalbumin, (5) chymotrypsinogen A, (6) ribonuclease A, and (7) insulin. A cadmium glutathione complex was also used for the Sephadex G-50 column. Two to four reference proteins were fractionated on each column preceding each filtration experiment. A standard curve was derived from a plot of log molecular weight vs. elution volumes.[43] Elution volumes (V_e) were monitored at 280 and 254 nm.

Before each experiment the columns were treated with the elution buffer containing (0.001M) *ortho*-phenanthroline to remove contaminating metal ions.

Isolation of the Cd^{2+}-Binding Proteins of the Lung and Kidney

Samples of the nondiffusible, nonultrafilterable material from lung or kidney were applied to a column packed with Sephadex G-75 (fine grade) equilibrated with 0.02M Tris–HCl buffer, pH 8.6. The effluent from the column was monitored at 253.7 nm and collected in 3- to 5-ml aliquots. Samples were run from bottom to top at a flow rate of 30 ml/hr. All experiments were performed at 4°C. The fractions were analyzed for metal and protein[44] where necessary and were pooled according to the metal-ion elution pattern(s). The pooled fractions were concentrated with an ultrafiltration unit equipped with a UM-2 or UM-10 filter

(depending on the molecular weight of the fraction) before subsequent reapplication on the succeeding columns. Gel filtration experiments conducted on Sephadex G-50 were performed with 0.02M potassium phosphate buffers, pH 7.4. All fractions that were not concentrated and reapplied to the succeeding column(s) were lyophilized and stored at −20°C. The results of several filtration experiments will be discussed.

Light Microscopy

Tissue samples from the two groups of animals (three experimental animals and three controls per group) exposed to CdO for 9 and 13 months were taken for evaluation.

For routine examinations, tissues were fixed in formalin, embedded in paraffin wax, and sectioned at 8 μm. The sections were stained with hematoxylin and eosin.

RESULTS AND DISCUSSION

There was a prolonged latent period before fibrosis of the lung was apparent by light microscopy.[4,5] For this paper, measurements were performed on the groups of animals exposed, respectively, to CdO aerosols for 9 and 13 months, as well as on their controls. There were no noticeable pathological changes due to the perfusion/lavage treatment of the lungs. At the light microscope level, the present observations correspond to those previously described.[4,5] More specifically, in the lung, fibrosis of the wall was present, extending into the adjacent alveoli. There was also infiltration by lymphocytes. Some macrophages were scattered throughout the alveoli. One rat showed a more advanced fibrosis. Occasionally proliferative lesions were seen in all exposed lungs. These consisted of small papilloma-like excrescences into the lumen of the terminal bronchiole. They were made up of fibrous tissue with lymphocytic infiltrates. The surface was covered by flat epithelium. Significant fibrosis of the pleura was absent. Lungs of the control rats showed the usual histologic structure without pathologic alterations.

The microscopic examination of the lung of all animals submitted after 13 months' exposure revealed an increase in the fibrosis of the respiratory bronchioles when compared with animals exposed for 9 months. Special stains for fibrous tissue and muscle tissue showed that the fibrous tissue was collagenous. No additional significant differences were present.

The microscopic examination of the kidneys using H & E stained sections revealed focal interstitial nephritis with rare foci of fibrosis after 9 months exposure. No additional changes were observed after 13 months that could be attributed to CdO. A slight thickening of the Bowman's capsule was observed in all animals, but it is a common feature in rats at 15 to 16 months.

Previous work in these laboratories has established that, once animals are exposed to the aerosols for several weeks, the majority of the cadmium is associated with the soluble supernatant of the cells.[35] After 9 months, cadmium levels begin to reach a plateau in the lung. The approach to equilibrium concentrations of cadmium in the lung after this period has been tentatively correlated with the appearance of lung pathology, which was only evident after this exposure. Light microscopic examination of the kidneys of these animals indicated only isolated pathological changes, and equilibrium concentrations were not apparent in the kidney even after 13 months' exposure.

Biochemical fractionation of both organs has demonstrated some similarities and differences. Half the homogenates from 10 lungs and 10 kidneys were used for the preparation of the material subsequently described.

Dialysis experiments lasting 24 hr were performed on the 100,000 × *g* supernatant fractions of both lung and kidney from the 9-month exposure period. For this exposure period, there were maximum losses of about 10 to 30% of the cadmium, 18% of the available zinc, and 30 to 45% of the copper from the lung supernatant. In the kidney, similar treatment yielded a 45% loss of cadmium, a 50% loss of zinc, and a 55% loss of copper (Table 1).

When the dialysates were separated on Sephadex G-75, the total recovery was 90 to 100% of that applied. The elution profiles of the supernatants from a 9-month exposure group are shown in Figs. 1(a) and 2(a). Chromatography of these dialysates indicated that cadmium was primarily associated with a low-molecular-weight component of about 12,500 in both organs (V_e = about 325 ml). A distinct difference in the relative ratios of metals was observed between the lung and kidney for this fraction. In the lung the cadmium/zinc/copper mole ratio was 38 : 8 : 1, whereas in the kidney a considerable redistribution of the metals, presumably through metabolic processes, was evident in the respective mole ratios of 5.3 : 1 : 4.6 for the same fraction. These ratios are expected to change somewhat with further purification. The apparent cadmium/zinc/copper mole ratio in the kidney may be a reflection of the presence of two isostructural proteins as has been previously observed.[30] In the lung, this molecular-weight fraction represented 83% of the cadmium, 21% of the zinc, and 38% of the copper put on the column. For the kidney, 45% of the cadmium, 8% of the zinc, and 42% of the copper put on the column were recovered in this fraction. The molar ratios of titratable sulfhydryl groups[29] to metals in this fraction were as follows for the respective organ fractions:

	$\frac{\mu M\ (SH)}{\mu M\ Cd}$	$\frac{\mu M\ (SH)}{\mu M\ Zn}$	$\frac{\mu M\ (SH)}{\mu M\ Cu}$	$\frac{\mu M\ (SH)}{\mu M\ (Cd + Zn + Cu)}$
Lung	2.59	13.89	65.97	2.11
Kidney	4.36	21.20	5.12	2.12

A higher-molecular-weight cadmium-containing component was observed in the lung. This fraction represented 10% of the total cadmium, 40% of the zinc,

TABLE 1

REPRESENTATIVE YIELDS OF CADMIUM-BINDING COMPONENTS IN LUNG AND KIDNEY AFTER 9 MONTHS' CdO INHALATION EXPOSURE

Fraction	Controls				Exposed			
	Cd, %	Zn, %	Cu, %	Protein, %	Cd, %	Zn, %	Cu, %	Protein, %
LUNG								
Supernatant	100	100	100	100	100	100	100	100
Supernatant after dialysis vs. Na_2CO_3	<limit	53	84.5	82.1	74.3	81.7	56.3	102.3
Sephadex G 75 Filtration								
Fraction 1, V_e = 120 to 180 ml	<limit	9.3	13.3	66.2	7.5	32.3	12.8	84.7
Fraction 2, V_e = 180 to 230 ml	<limit	8.6	16.3	5.0	1.9	11.7	20.6	11.9
Fraction 3, V_e = 230 to 280 ml	<limit	6.9	17.1	3.0	4.7	17.0	21.5	3.3
Fraction 4, V_e = 280 to 370 ml	<limit	<limit	<limit	3.1	51.3	1.4	0.6	2.3
Fraction 5, V_e = 370 to 475 ml	<limit	28.2	37.6	4.7	0.9	5.2	0.1	0.1

KIDNEY								
Supernatant	100	100	100	100	100	100	100	100
Supernatant after dialysis vs. Na_2CO_3	100	44.6	89.5	74.4	55.0	48.7	45.3	70.8
Sephadex G-75 filtration								
Fraction 1, V_e = 120 to 180 ml	6.1	20.6	3.8	50	4.5	16.4	5.2	3.75
Fraction 2, V_e = 180 to 230 ml	2.8	11.5	11.0	10.3	6.0	6.0	6.1	1.1
Fraction 3, V_e = 230 to 280 ml	19.6	5.9	16.6	3.0	25.4	3.7	19.1	25.3
Fraction 4, V_e = 280 to 370 ml	71.5	6.5	57.9	6.2	3.9	1.9	2.9	17.4
Fraction 5, V_e = 370 to 475 ml	<limit	<limit	<limit	4.9	3.4	20.6	1.0	23.1

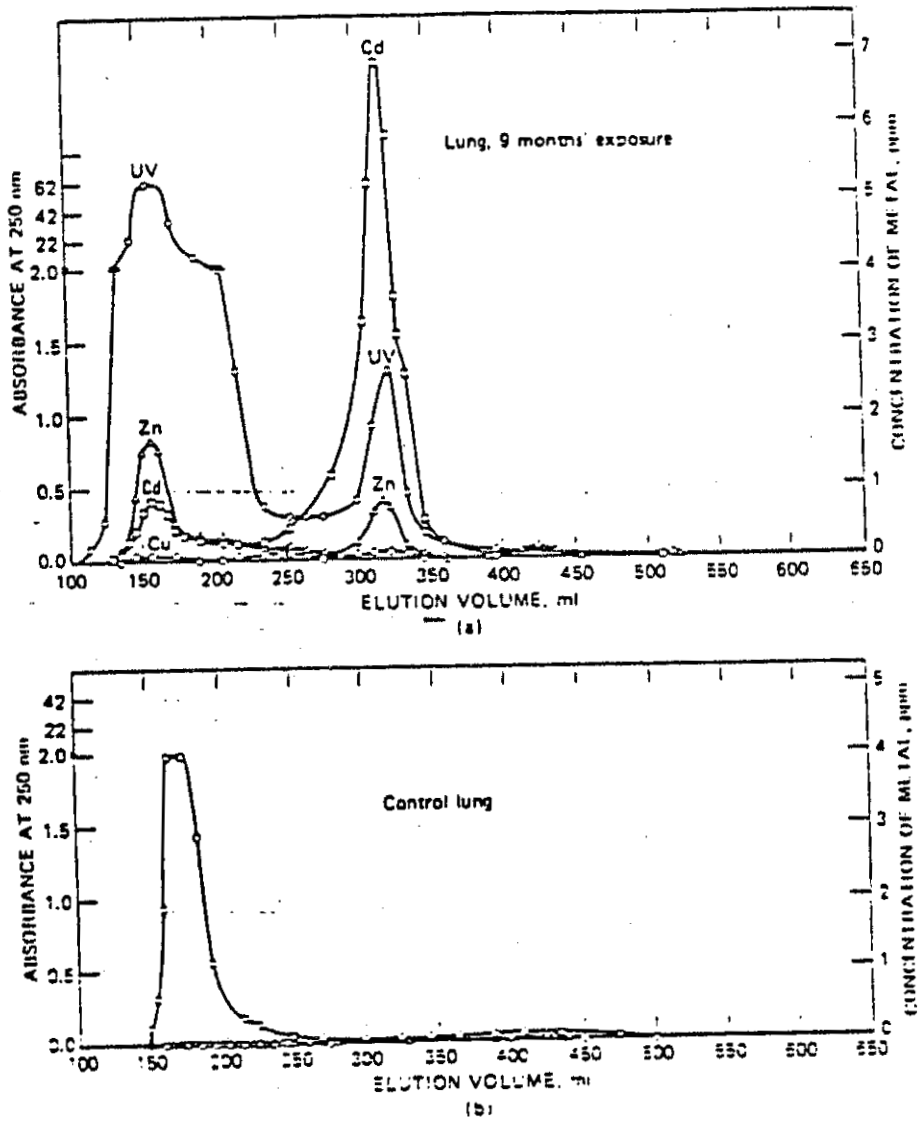


Fig. 1 Sephadex G-75 gel elution profiles of the supernatant fraction from the lungs of rats (a) exposed to CdO aerosols (347.5 mg/m^3) for 9 months and (b) their paired controls. The column (82 by 2.5 cm) was eluted at 4°C with 0.02M Tris–HCl buffer, pH 8.6, at flow rates of 30 ml/hr. Fractions (6 ml) were collected and analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○), and protein (○), optical density at 250 nm. Both supernatants were dialyzed at 4°C before gel filtration. The Cd^{2+} concentration of the dialysates were (a) 20.55 μg/ml and (b) 0.008 μg/mL

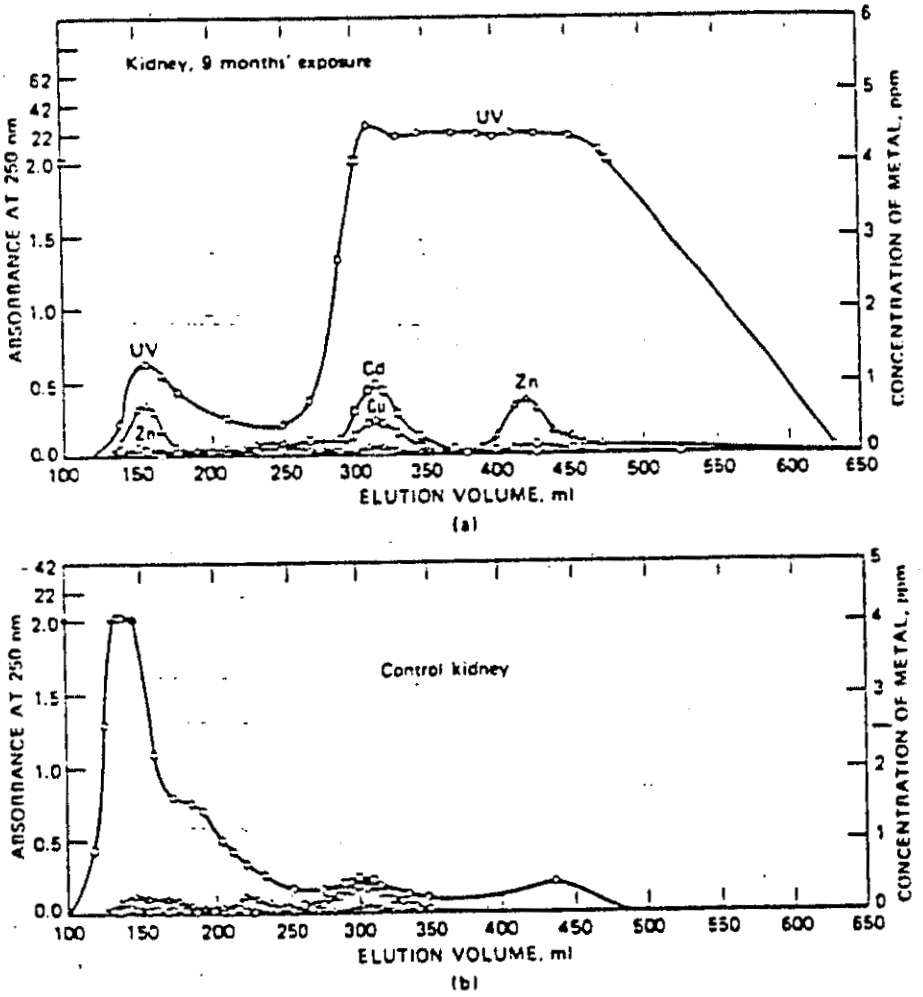


Fig. 2 Sephadex G-75 gel elution profiles of the supernatant fraction from the kidneys of rats (a) exposed to CdO aerosols (347.5 mg/m^3) for 9 months and (b) their paired controls. The column (82 by 2.5 cm) was eluted at 4°C with 0.02M Tris–HCl buffer, pH 8.6, at flow rates of 30 ml/hr. Fractions (6 ml) were collected and analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○), and protein (○), optical density at 250 nm. Both supernatants were dialyzed at 4°C before gel filtration. The Cd^{2+} concentration in the dialysates were (a) 5.55 μg/ml and (b) 3.22 μg/ml.

and 23% of the copper. The molecular weight was 90,000 or above since the component eluted close to the void volume. A similar component was present in the kidney in lesser quantities. Cadmium has been previously observed to be bound to high-molecular-weight components in the liver following high injection levels.[26] Whether this fraction represents "spillage" from the sequestering metallothionein or initial binding to a large protein before synthesis of

metallothionein[19] cannot be determined at present. The synthesis of almost exclusively cadmium–thionein in the kidneys of rabbits has been reported.[28] It is interesting that, under the conditions of the present experiment, which represent chronic exposures, a fraction similar to cadmium–thionein (by virtue of its molecular weight, its metal and sulfhydryl concentration, and its ultraviolet extinction coefficient ratio) was only observed in the lung. In the kidney the analogous fraction contained appreciable quantities of copper.

Dialyzable material from the kidney representing 30% of the total supernatant Cd^{2+} and 20% of the total protein was chromatographed on a Sephadex G-25 column. The cadmium-binding fractions separated into two peaks: fraction 1, eluting in the void volume (6% total supernatant cadmium) and fraction 2, eluting at 32 ml (20% total supernatant cadmium). Both fractions were concentrated and rechromatographed on G-50 (Fig. 3), where additional separation occurred.

Figure 3(a) is the elution profile of the higher-molecular-weight fraction 1 from G-25. Two cadmium-binding components are apparent. The first component, with a molecular weight of >10,000, has $\lambda_{max.}$ at 275 and 405 nm ($\epsilon_{max.}$, 405). The cadmium recovered was 30% of that put on the column (1.5 to 2% total supernatant cadmium). *The second component*, with V_e = 45 ml and a molecular weight of about 4500, has $\lambda_{max.}$ at 225 and 273 nm ($\epsilon_{max.}$, 225) and appears to be a binary mixture since the $\lambda_{max.}$ at 273 nm peaks at V_e = 49 ml whereas [Cd] is at a maximum at V_e = 44 ml. The cadmium recovered was 60% of that put on the column (about 3% total supernatant cadmium).

Similar ultraviolet absorbing components appear in the elution profile shown in Fig. 3(b), which originated as the lower-molecular-weight fraction 2 from G-25. The third component, eluting at 64 ml (molecular weight of about 700) contains 25% of the cadmium recovered from the column ($\lambda_{max.}$, 225, 264, and 290; $\epsilon_{max.}$, 225), and, on the basis of its ultraviolet spectrum, it appears to be a purified constituent of the binary mixture eluting at 50 ml in Fig. 3(a).

Fractionation of control-animal organs was identical to that of the preceding description. After a 24-hr dialysis experiment, 45% of the available zinc and 15% of the available copper were removed from the supernatant (100,000 × *g* fraction) of the control lung. The total metal concentration at this point was 0.18 μg/mg of protein. In the kidney, similar treatment yielded no loss of cadmium, a 55% loss of zinc, and a 10% loss of copper (Table 1). The total metal concentration was 0.67 μg/mg of protein at this stage.

The Sephadex G-75 elution profiles for the control animals are shown in Fig. 1(b) and 2(b). The vast majority of the protein in control lung and kidney elutes in the void volume of the column, although a small amount of material in the *12,000-molecular-weight range is observed in the kidney.*

Further fractionation of the high-molecular-weight lung proteins on Sephadex G-100, with similar treatment to that described in Fig. 4(b) (flow rate, ml/hr), yielded two peaks: (1) a low-molecular-weight (<25,000) component that represented the majority of the protein and (2) a high-molecular-weight

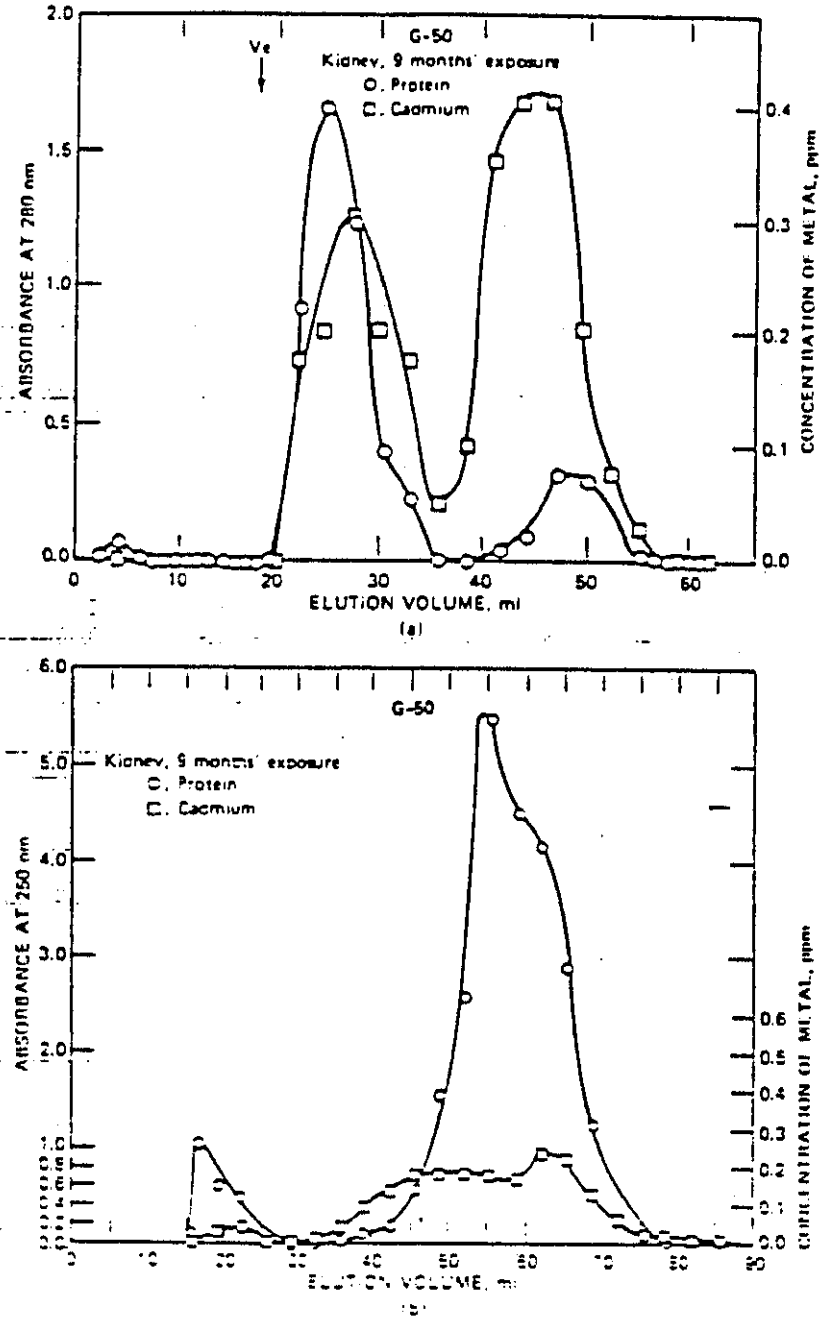


Fig. 3 Sephadex G-50 separation of dialyzable components from the kidneys of rats exposed to CdO for 9 months. The column dimensions were 1.5 cm by 30.0 cm. Elutions were carried out at 4°C with (a) 0.025 M phosphate buffer pH 7.1 and (b) 0.025 M Tris–HCl buffer pH 7.3 at flow rates of 18 ml/hr (3 ml/fraction). (a) Material collected from fractions 4 to 6 of the preceding G-25 filtration (4.67 μg Cd^{2+}/ml). (b) Material collected from fractions 7 to 15 at the preceding G-25 filtration (11.0 μg Cd^{2+}/ml) (see text).

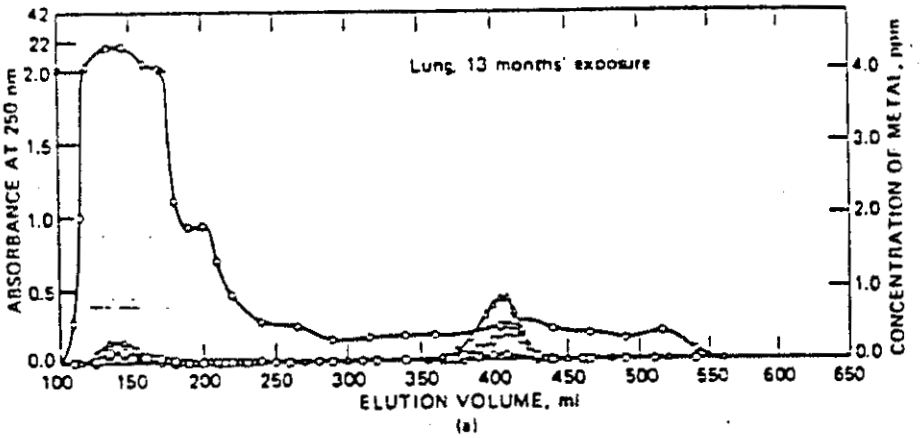
(>150,000) component that was present in small quantities. The kidney proteins have not been purified on G-100 to date.

Because the interstitial disease observed by light microscopy was only moderately advanced at the end of 9 months, one experimental group was left in the chamber for 13 months. Fractionation of these organs was identical to that of the preceding description except that dialysis was performed through the use of an ultrafiltration apparatus equipped with a UM-2 membrane (molecular weight cutoff, 1000).

Dialysis via ultrafiltration of the lung-soluble supernatant resulted in 60% of the available cadmium, 40% of the available zinc, and 25% of the available copper being removed (Table 2). The metal concentration in the remaining dialysate was 0.27 $\mu g/mg$ of protein. Identical treatment of kidney supernatant removed only 18% Cd^{2+}, 20% Zn^{2+}, and 10% of the available Cu^{2+} (Table 2). The metal concentration in the remaining dialysate was 0.74 $\mu g/mg$ of protein. The G-75 and G-100 elution profiles for the dialysates of each organ are shown in Figs. 4 and 5. As can be deduced from Table 2, the total recovery of Cd^{2+} from the G-75 column was 58% of that applied for the lung and 100% of that applied for the kidney.

The most remarkable change noted in the lung supernatant was the virtual absence of a fraction with a molecular weight corresponding to that of metallothionein. The two cadmium-binding fractions present correspond to molecular weights of >150,000 (void volume elution) and 3900 (fractions 1 and 4, respectively, in Table 2). Chromatography of the first on G-100 [Fig. 4(b)] resulted in further separation of this high-molecular-weight fraction into two metal-containing components, each representing 5 to 6% of the original supernatant cadmium if we adjust the figures to account for the low G-75 column recovery. Fraction 4, eluting at 410 ml from G-75, represented 22% of the total cadmium in the supernatant and had a molecular weight of about 4000 with $\epsilon 250/280 = 1.5$, as did the small fraction eluting at 425 ml from similar treatment of the 9-month lungs [see Fig. 1(a)].

The G-75 gel filtration of the kidney dialysate separated approximately the same number of metal-binding components as were observed at 9 months' exposure, although the relative proportions were altered [Fig. 5(a)]. After 13 months, 44% of the available Cd^{2+}, 32% of the available Cu^{2+}, and 1% of the available Zn^{2+} were recovered in the low-molecular-weight metallothionein-like fraction 3 (molecular weight of 10,500 with $\epsilon 250/280 = 1.6$). Table 2 lists the representative recovery of each metal and the total protein in the individual fractions from the columns. Thus fraction 1 (V_e = 135 to 223 ml) contained 18%, fraction 2 (V_e = 223 to 290 ml) contained 10%, and fraction 4 (V_e = 360 to 475 ml) contained 9% of the total supernatant cadmium. Fraction 1 was concentrated and further separated on Sephadex G-100 [Fig. 5(b)]. Cadmium recovery was 85% of that applied. Whereas the lung appears to possess two high-molecular-weight metal-binding proteins [Fig. 4(b)], the kidney appears to contain 3 or possibly 4, together totaling 16% of the available Cd^{2+}. The small



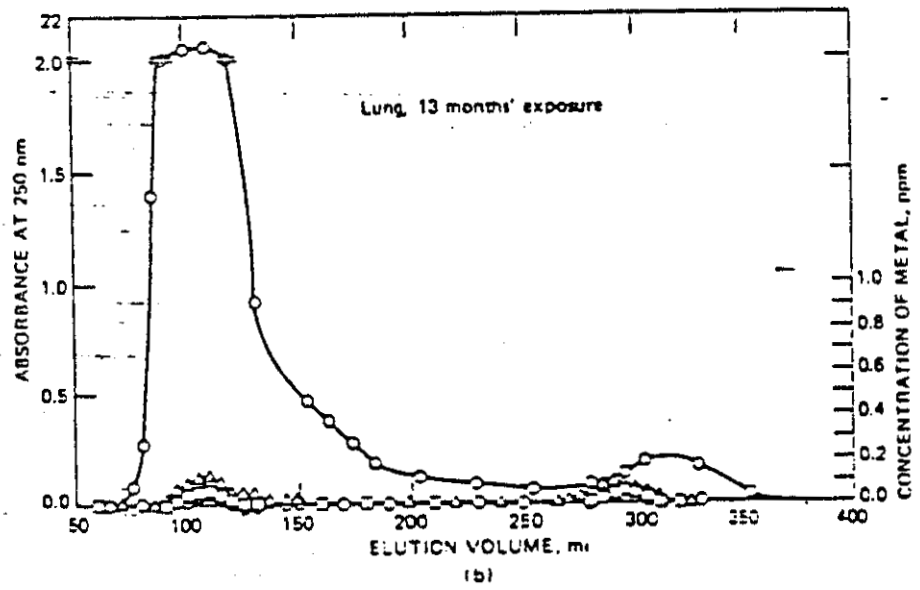


Fig. 4 Sephadex gel elution profiles of the supernatant fractions from rat lungs eluted at 4°C with 0.02M Tris–HCl buffer, pH 8.6. Dialysis was performed at 4°C before gel filtration. Fractions collected were analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○) and protein (●), optical density at 250 nm. (a) Dialysate (1.88 μg Cd/ml) applied to G-75 column (82 by 2.5 cm), flow rate 30 ml/hr, 5 ml/fraction. (b) Fraction 1 (116 to 235 ml elution) from G-75 column (0.37 μg Cd/ml), applied to Sephadex G-100 column (64 by 2.5 cm), flow rate 6 ml/hr, 5 ml/fraction. The exposure level was 289 $\mu g/m^3$ for 13 months.

TABLE 2

REPRESENTATIVE YIELDS AND DISTRIBUTION OF METAL BINDING COMPONENTS IN LUNG AND KIDNEY AFTER 13 MONTHS' CdO INHALATION EXPOSURE

Fraction	Exposed lung				Exposed kidney			
	Cd, %	Zn, %	Cu, %	Protein, %	Cd, %	Zn, %	Cu, %	Protein, %
Supernatant	100	100	100	100	100	100	100	100
Supernatant after dialysis vs. Na_2CO_3	38.6	60.8	74.4	76.5	82.2	78.4	92.4	98
Sephadex G 75 Filtration								
Fraction 1, V_e = 116 to 190 ml	7.2	11.0	30.3	59.8				
= 135 to 223 ml					18.4	13.0	12.7	57.8
Fraction 2, V_e = 190 to 240 ml	<limit	<limit	8.4	9.9				
= 223 to 290 ml					10.2	8.8	11.7	17.7
Fraction 3, V_e = 240 to 360 ml	<limit	<limit	<limit	1.6				
= 290 to 360 ml					44.2	1.4	32.4	1.7
Fraction 4, V_e = 360 to 435 ml	15.2	31.2	22.7	0.6				
= 360 to 475 ml					9.4	24.9	<limit	6.7

Fraction 5, V_e = 415 to 568 ml = 475 to 530 ml	<limit	<limit	<limit		0.7		<limit	<limit	<limit	5.9
Sephadex G-100 filtration,										
Fraction 1 above										
Fraction 1, V_e = 93 to 111 ml = 70 to 150 ml	3.4	6.5	6.8	31.7						
Fraction 2, V_e = 111 to 200 ml = 150 to 200 ml	<limit	1.1	3.4	8.1		11.9	9	9.2	35.0	
Fraction 3, V_e = 200 to 274 ml = 200 to 245 ml	<limit	<limit	<limit	2.0		0.5	<limit	1.2	1.0	
Fraction 4, V_e = 274 to 304 ml = 245 to 290 ml	2.7	3.8	1.7	5.3		<limit	<limit	<limit	0.5	
Fraction 5, V_e = 304 to 360 ml	<limit	<limit	<limit		6.2	5.3	3.9	1.2	0.7	
						<limit	<limit	<limit	0.7	

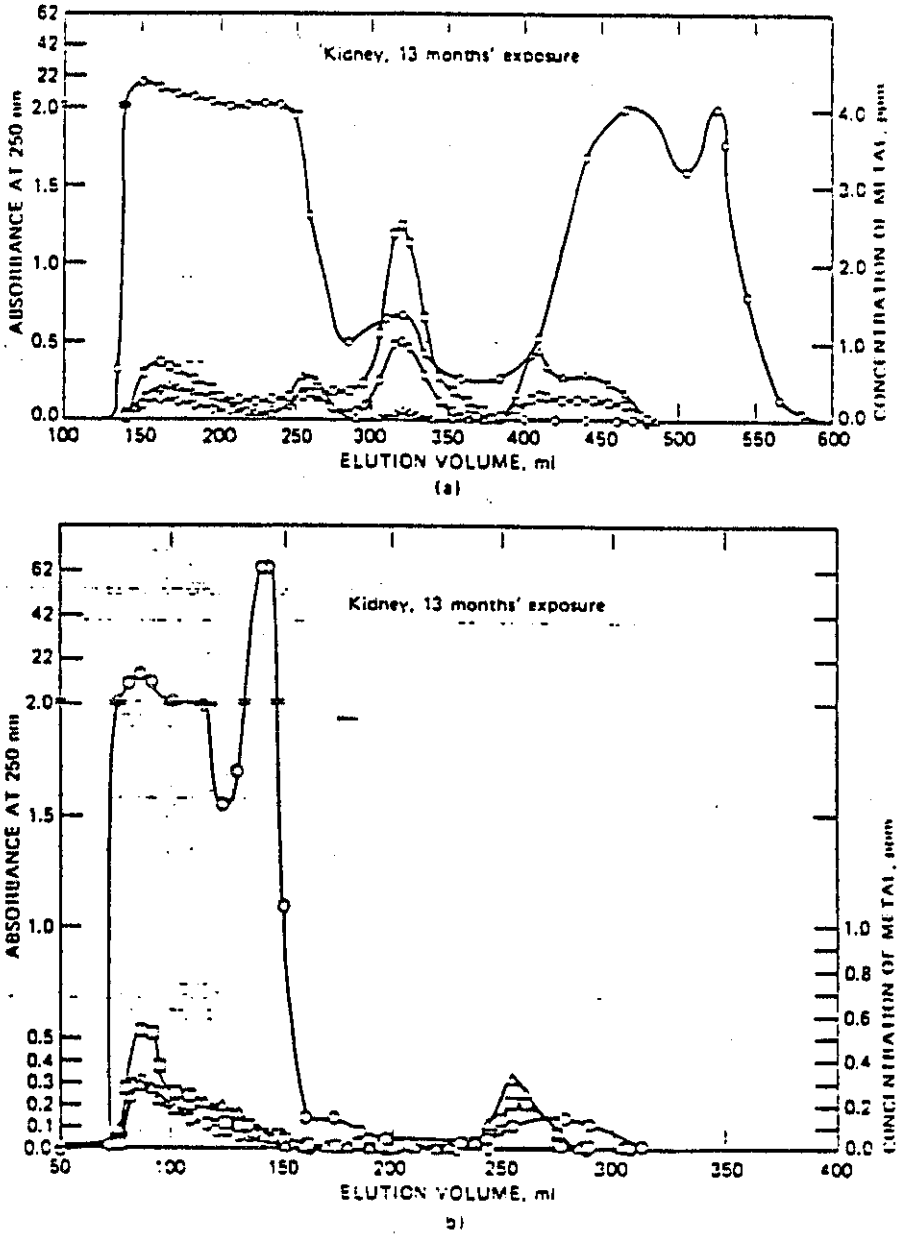


Fig. 5 Sephadex gel elution profiles of the supernatant fractions from rat kidneys eluted at 4°C with 0.02*M* Tris–HCl buffer pH 8.6. The supernatant was dialyzed at 4°C before gel filtration. Fractions collected were analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○), and protein (○), optical density at 250 nm. (a) Dialysate (5.37 μg Cd/ml) applied to G-75 column (82 by 2.5 cm), flow rate 30 ml/hr, 5-ml fractions collected. (b) Fraction 1 (135.5 to 223.5 ml elution) from G-75 column (4.30 μg Cd/ml), applied to G-100 column (64 by 2.5 cm), flow rate 4 ml/hr, 3-ml fractions collected. The exposure level was 289 μg/m³ for 13 months.

fraction with an elution volume of about 250 to 300 ml in both Figs. 4(b) and 5(b) corresponds to a molecular weight of <25,000.

We call attention to the pathology of the lungs from this latter group of animals, which were previously described as being in a definitive state of fibrosis. Because the lungs are quite fibrotic, homogenization of the tissue is very difficult and the yield of extractable soluble protein is relatively low. Likewise, the cadmium concentration (2.36 μg/ml) in the soluble supernatant is much lower than that measured in the lungs of animals exposed for only 9 months (5 to 13 μg/ml). This does not explain, however, the absence of low-molecular-weight (10,000 to 12,000) components or the presence of a substantial percentage of dialyzable cadmium. Further work is in progress.

ACKNOWLEDGMENTS

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Organ Distribution and Protein Binding of Cadmium in Autopsy Material from Heavy Smokers

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Male heavy smokers were autopsied within 3 days postmortem. Samples from kidney, liver, and lung were taken for analysis of cadmium levels and degree of protein binding within the cytosolic fraction. The levels in lung, liver, and kidney were 0.50 ± 0.35 ($\bar{X}$ ± SEM), 2.21 ± 0.63, and 17.4 ± 8.8 μg cadmium/g wet weight tissue, respectively. In liver and kidney, approximately 75% was bound to a low-molecular-weight protein whereas the corresponding figure for the lung cytosolic fraction was 56%, a difference being statistically significant ($P < 0.05$). After concentration of the low-molecular-weight cadmium-binding protein(s) (CdBP) by ultrafiltration and preparative isoelectric focusing in a granulated gel, the cadmium appeared in one single band with pI values of 5.8 (lung and liver) and 6.0 (kidney), respectively. It is therefore concluded that human lung exposed to cadmium, in this case via cigarette smoke, contains a CdBP, which binds cadmium. The relative degree of binding is less in lung than in liver or kidney, implicating that the metal could be more toxic to the lung than to liver or kidney, as the protein probably serves a role in detoxifying cadmium.

INTRODUCTION

Prolonged exposure to cadmium has been shown to cause accumulation of the metal mainly in the kidneys, which probably also is the main target for the toxic action (Baader, 1952; Bonnell, 1955; Kazantsis *et al.*, 1963). Pulmonary emphysema has also been shown to be developed in workers after prolonged high-dose exposure to cadmium by inhalation of contaminated air (Friberg *et al.*, 1974). One possible mechanism underlying the development of pulmonary emphysema involves proteolytic attack on the tissue by endogenous proteolytic enzymes, because proteases, instilled into the lung through the trachea, produce emphysema-like lesions (Gross *et al.*, 1965). The emphysema caused by inhalation exposure to cadmium could thus be mediated by proteolytic enzymes from cells in the lung. The studies by Henderson and collaborators have not clearly demonstrated such an effect by cadmium, however, when the metal was instillated as a solution into the trachea (Henderson *et al.*, 1979).

A protein with specific cadmium-binding ability, metallothionein, has been demonstrated mainly in liver and kidney cytosolic fractions. This protein plays a central role in the intracellular metabolism of cadmium (Nordberg *et al.*, 1971) by chelating the metal ions in the tissue, and in this way it is believed to protect sensitive metabolic functions of the cells. Cadmium-binding protein(s) similar to

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TABLE I
INDIVIDUALS AUTOPSIED

Initials	Age (years)	Time between death and autopsy (days)	Primary cause of death
K.K.	78	1	Bronchial pneumonia
B.-O.E.	69	4	Cardiac infarction
B.L.	71	2	Pulmonary edema
ÅR.	65	3	Subarchnoidal bleeding
E.S.	78	3	Pulmonary cancer with metastases

methallothionein have been detected in syrian hamster lung (Benson and Henderson, 1980) and in several cell lines derived from pulmonary tissue (Cox and Waters, 1978; Hart and Keating, 1980; Hildebrand and Cram, 1979). The proteins have been shown to be synthesized de novo on exposure to an aerosol of cadmium chloride (Post *et al.*, 1982). An alternative explanation to that of proteolytic attack on the lung, could either be that the lungs in man do not synthesize the CdBP in lung at exposure, or that the amount is not sufficient to bind all the accumulated metal in the lungs. In both cases, the Cd^{2+} ions would be free to excert their toxic action on the tissue. The aim of the present investigation was therefore (1) to see whether man exposed to cadmium via the airways has detectable metallothionein-like proteins in the lung and (2) whether the Cd^{2+} ions persist in the lung tissue in their free or bound form. Heavy smokers were used as source for tissue specimens postmorten, as this category has an elevated body burden of cadmium due to contamination of the tobacco (Elinder *et al.*, 1976).

MATERIALS AND METHODS

Five heavy smokers autopsied at the Department of Clinical Pathology at the Linköping University Hospital were investigated. The age and cause of death are listed in Table 1. The time between death and autopsy was 3 days (mean) with a range of 1 to 4 days. The bodies were kept at +4°C until autopsy was performed. In subject E.S., who had a pulmonary cancer, the material used in this study was noncancerous. The material was frozen and kept at −20°C until processed further. A freeze-pressing technique (Edebo, 1960) was used for homogenization. A buffer containing 0.25 M sucrose, 0.01 M Tris–hydroxymethyl–aminomethane (Tris), and adjusted to pH 8.6 with hydrochloric acid, was added in equal weight to the tissue before the homogenization. The homogenate was centrifuged at 150.000*g* to isolate the cytosolic fraction of the tissue. Samples of this and the crude homogenate were saved at −20°C for later analysis of protein content and cadmium level. A sample of the cytosolic fraction of lung, liver, and kidney from each individual was applied to a 2.8 × 65-cm Sephadex G50 column. The samples were eluted with a 0.01 M Tris–HCl buffer (pH 8.6) containing 0.02% sodium azide. Samples of 11 ml were collected to later be monitored for protein, measuring the absorbance at 280 nm in a Pye–Unicam SP-500 uv spectrophotometer. The cadmium levels were determined using an Instrumentation Laboratory 551 atomic absorption spectrophotometer equipped with a graphite furnace (Instru-

mentation Laboratory 555) and an automatic sampler (Instrumentation Laboratory 254). The method gave acceptable signal-to-noise ratios down to 1 ng/ml sample. The samples from the column containing CdBP were pooled, concentrated using a Micropore UM2 ultrafilter, and later characterized further by isoelectric focusing.

Flat-bed isoelectric focusing was carried out with the use of an LKB Multiphore apparatus coupled to an LKB power supply (model 2103). Cold tap water was used in order to maintain the cooling plate and the gel at a temperature of +10°C. The electrofocusing was run in a granulated gel bed composed of 6.6% Ultrodex (LKB) and 2% carrier ampholytes (LKB Ampholines) covering a pH range of 3.5–10.0. Samples of 1.0 ml concentrated and pooled CdBP from the individuals were mixed with the gel slurry before being added to the gel plates. The electrofocusing was run for approx 22 hr at a constant power of 5.2 W with an initial voltage gradient of 20 V/cm. After completion, a grid was applied to the gel, dividing it into 30 fractions. The gel from each section was removed, vortexted in a plastic tube with 1.0 ml of distilled water, the contents were cooled to +10°C, and the pH was measured with a combined glass/calomel electrode. The gel slurry was then filtered to remove the solid matrix and the liquid phase assayed for cadmium content.

RESULTS

The individuals examined in this study all had their highest levels of cadmium in the kidneys, followed by the liver and lungs (Table 2). The kidneys also showed a larger variation in the cadmium levels than the other two organs. The levels in kidney varied between 9.1 and 30.4 μg/g wet weight tissue, while the corresponding values in liver and in lung were 1.3–2.8 and 0.2–1.1 μg/g, respectively. Figure 1 shows three individual curves from the Sephadex G50 column. Part of the cadmium eluted from the column in the high-molecular-weight protein peak, and part of it at an elution volume around 1000 ml, where no peak was found at 280 nm, indicating that the cadmium-binding protein(s) in this region were similar to metallothionein in having no aromatic amino acids. The value of the relative distribution of cadmium between the high-molecular-weight protein (HMWP) as estimated from the Sephadex G50 chromatography and the CdBP similar to metallothionein was larger in lung then liver and kidney (Fig. 1 and Table 2). The CdBP peak (Fig. 1) from each organ was concentrated and 1 ml was applied to the isoelectric focusing bed as described under Materials and Methods. A single distinct peak of cadmium binding was found in all cases, having pI values of 5.8 (lung and liver material) and 6.0 (kidney material), respectively.

DISCUSSION

The individuals autopsied in the present investigation all had a level of cadmium in kidney around 30 mg/kg wet weight and less, which is far below the 200 mg/kg reported to cause toxic reactions in the kidney (Friberg *et al.*, 1974). It is, however, comparable to levels found by others in tissue from heavy smokers, where the tobacco has been shown to cause an additional source of cadmium to the general environmental background levels (Elinder *et al.*, 1976). The material

TABLE 2

TISSUE LEVELS OF CADMIUM AND THE RELATIVE BINDING TO THE LOW-MOLECULAR-WEIGHT CdBP AND THE HIGH-MOLECULAR-WEIGHT PEAK (HMWP) ACCORDING TO GEL FILTRATION (SEE FIG. 1).

	Individual					
	K.K.	B.-O.E.	B.L.	A.R.	E.S.	Mean ± S.E.M.
Lung						
Total amount (μg g wet weight tissue)	0.29	0.20	0.51	1.09	0.41	0.50 ± 0.35
Amount bound to CdBP (%)	31	62	68	65	52	56 ± 15
Amount bound to HMWP (%)	69	38	32	35	48	44 ± 15
Liver						
Total amount (μg/g wet weight tissue)	2.63	1.32	1.79	2.56	2.76	2.21 ± 0.63
Amount bound to CdBP (%)	66	63	88	80	81	*76 ± 11
Amount bound to HMWP (%)	34	37	12	20	19	*24 ± 11
Kidney						
Total amount (μg/g wet weight tissue)	9.07	16.73	20.83	30.39	9.86	17.00 ± 8.76
Amount bound to CdPB (%)	70	84	34	72	70	*76 ± 7
Amount bound to HMWP (%)	30	16	16	28	30	*24 ± 7

* $P < 0.05$ (paired t test) compared to lung.

in this study is far too small, however, to permit any conclusions to be drawn about the role of cigarette smoking in cadmium accumulation in man. However, the aim of the investigation was to give the binding characteristics of the metal to different protein fractions in lung, liver, and kidneys.

It is evident that lung tissue, as well as liver and kidney tissues, contain a protein in the low-molecular-weight range which binds cadmium to a high extent. Using gel filtration and isoelectric focusing, the protein(s) have been shown to have a molecular weight in the range of 10,000 Da, which is similar to metallothionein, and the absence of absorbance at 280 nm indicates another similarity. The pI values of the single peaks appearing at isoelectric focusing (Fig. 2) were 5.8 for lung and liver and 6.0 for kidney cytosolic CdBP. These are higher values than previously reported for rat and rabbit liver, from which two forms of metallothionein with pI values of 4.2 and 4.7 have been isolated (Cherian, 1974; Nordberg *et al.*, 1972). The possibility exists, though, that the single peak obtained in this study would have separated in two bands in a narrower pH gradient.

Metallothionein has been proposed to play an essential role in the detoxification of cadmium (Piscator, 1964). The present investigation demonstrates a protein component with low molecular weight. The separation characteristics of the protein, or possibly the protein complex of the lung cytosolic fraction are similar to

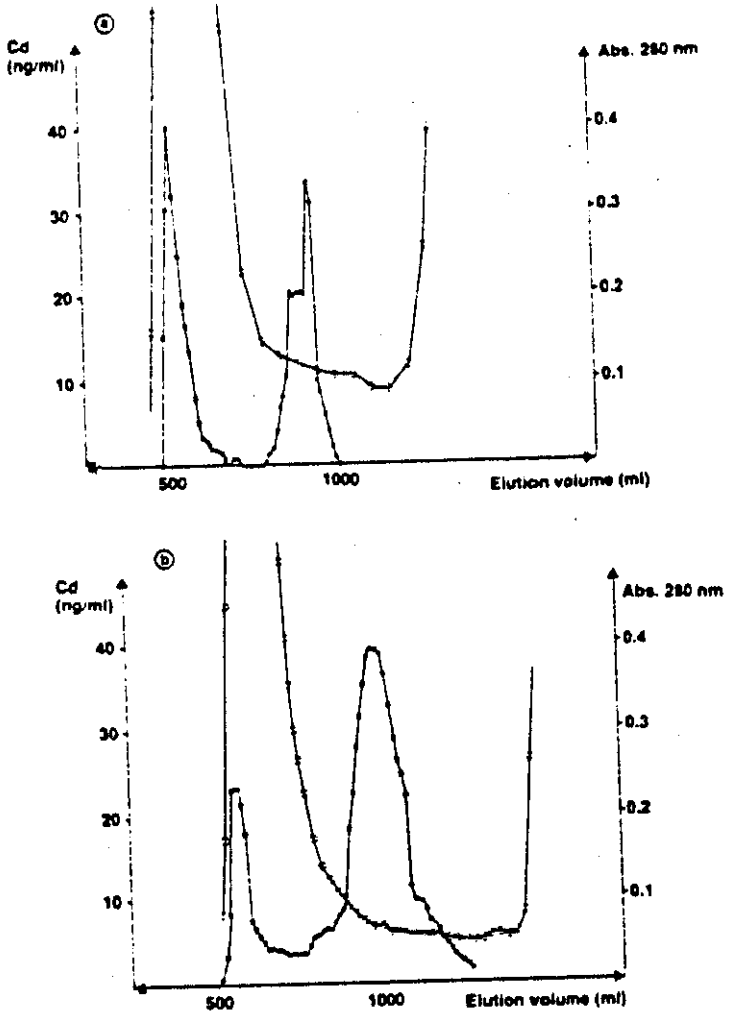


FIG. 1. Typical gel filtration chromatography in a 2.8 × 63-cm Sephadex column of tissue cytosolic fraction from one of the autopsied individuals (E.S.). (○) Denotes absorbance at 280 nm and (x), cadmium concentration in the fractions. (a) The elution pattern after application of 8.0 ml lung cytosolic fraction. (b) After 8.0 ml liver cytosolic fraction. (c) After 2.0 ml kidney cytosolic fraction.

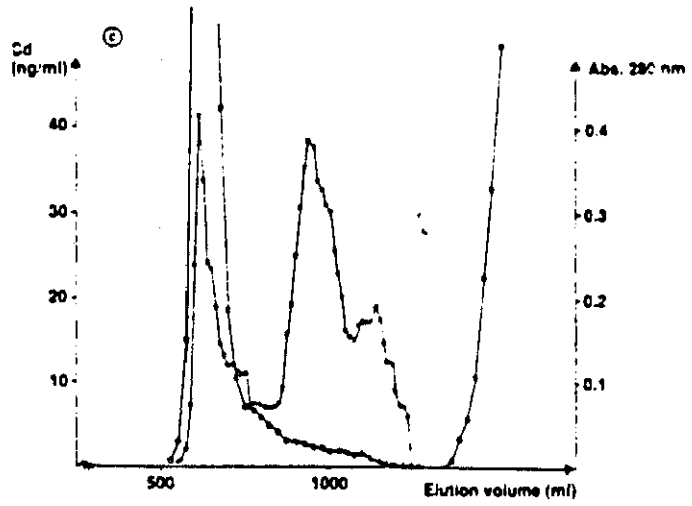


FIG. 1—*Continued*

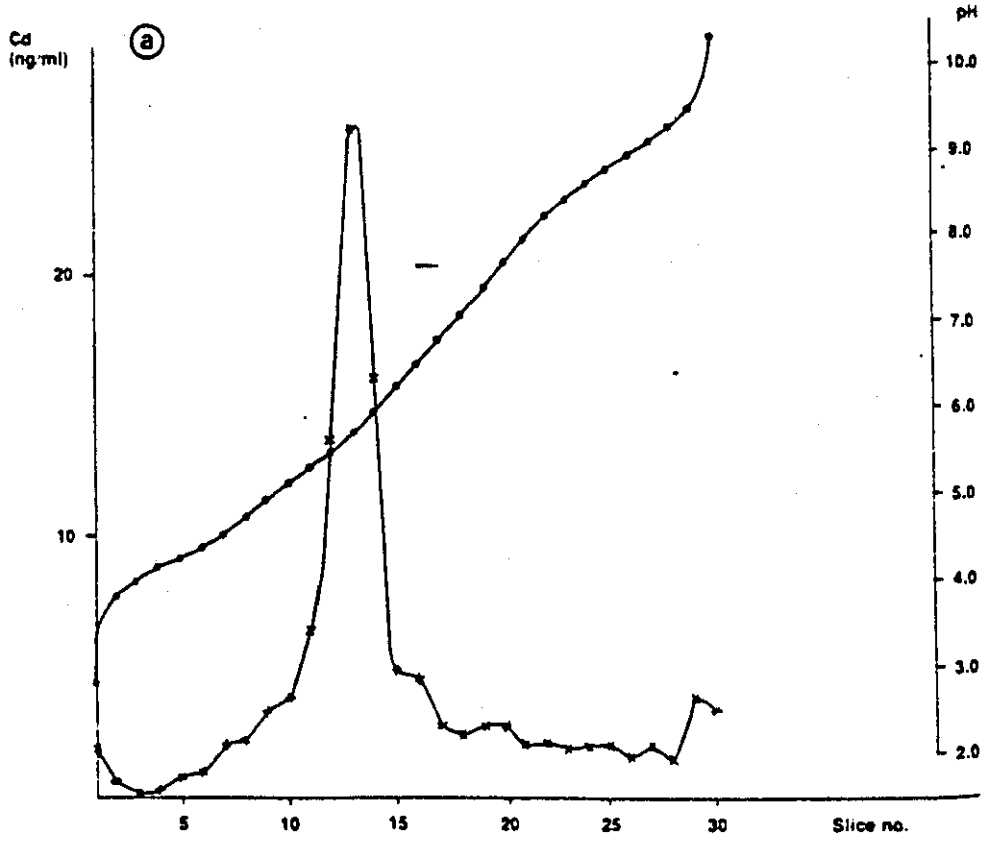
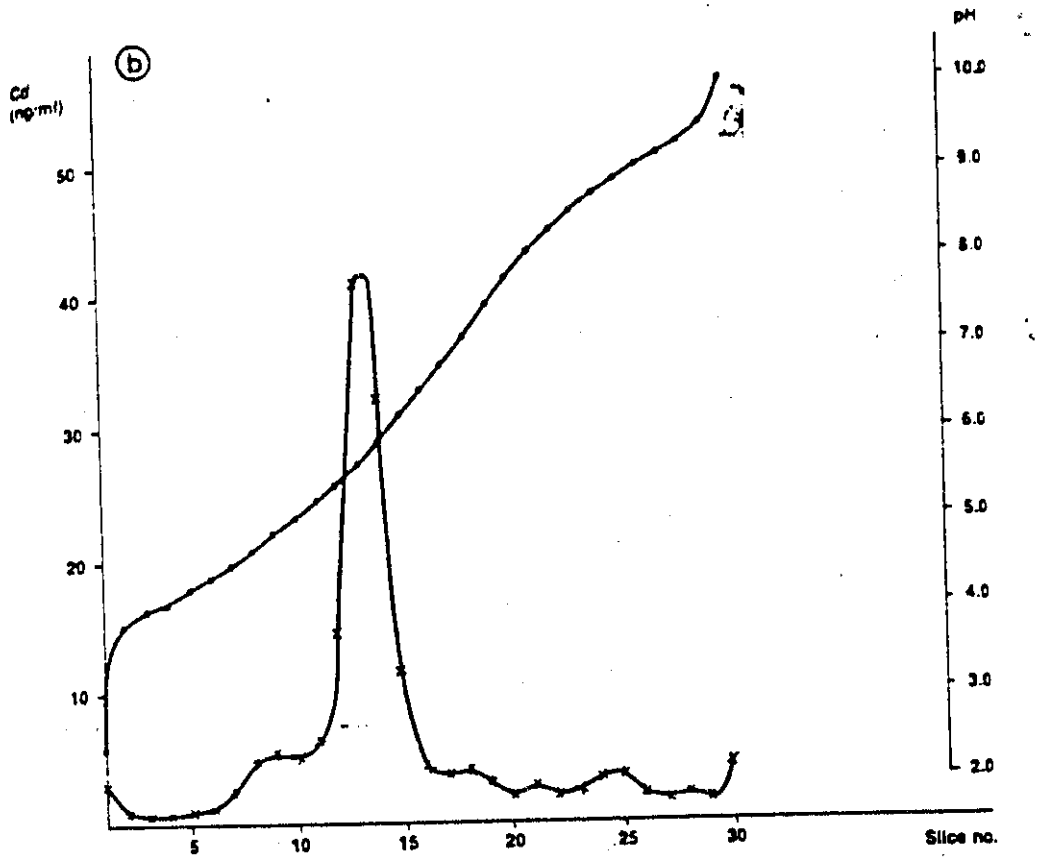


FIG. 2. Flat bed isoelectric focusing of 1.0 ml concentrated CdBP from all individuals pooled. (●) Denotes pH gradient and (x), cadmium concentration in extracts of the gels. (a) 1.0 ml lung CdBP containing 0.11 μg cadmium. (b) 1.0 ml liver CdBP containing 0.28 μg cadmium. (c) 1.0 ml kidney CdBP containing 1.90 μg cadmium.



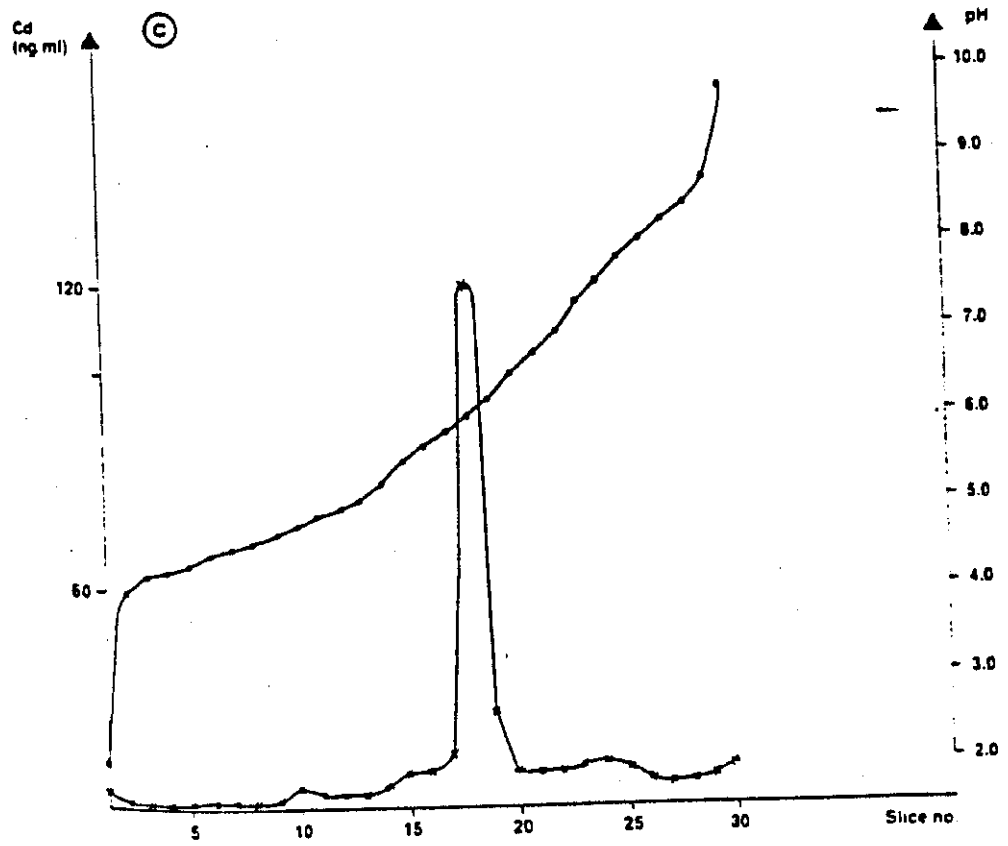


FIG. 2—*Continued*

that of liver or kidney. It is therefore likely that this protective factor against the toxic action of cadmium is present in human lung as well. It is interesting to note, however, that the cadmium-binding ability of lung tissue is less than that of liver or kidney tissue (Table 2). This could be an indication that the lungs are less capable to protect themselves against cadmium. A tempting speculation is therefore that individuals with subnormal capacity to synthesize the metallothionein-like protein are more susceptible to the toxic action of cadmium. A recently published study on the production of low-molecular-weight cadmium-binding proteins in the rabbit lung has shown this to be a rapid process, and that all cadmium is bound to the proteins within a few hours (Post *et al.*, 1982). The material taken postmortem in man was from old males, however, who had been exposed to large quantities of cigarette smoke. It is therefore not certain that their capacity to resynthesize the CdBP is sufficient. Another interesting aspect of this and other studies showing a lung CdBP, is that this CdBP could serve as a means of transporting the metal directly to the kidneys as has been indicated by others (Nordberg and Goyer, 1975; Johnson and Foulkes, 1980). Different capabilities to induce the protein could therefore give different body distribution of cadmium after deposition in the air passage.

ACKNOWLEDGMENTS

This work was supported by the Swedish Work Environment Fund, Grant 80/332. Dr. Bernt Boeryd, Department of Clinical Pathology, and Dr. Karl-Erik Magnusson, Department of Medical Microbiology, are gratefully acknowledged for their generous support.

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PACIFIC GAS AND ELECTRIC COMPANY

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August 20, 1986

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Comments on Cadmium Risk Assessment

Pacific Gas and Electric Company appreciates this opportunity to comment on the Air Resources Board (ARB)/Department of Health Services (DHS) June 1986 Cadmium risk assessment.

We recommend that the DHS' Part B risk assessment be revised to:

1. state that the data are consistent with a threshold below which there is no risk from exposure, and that the range of risk is zero to 12 cases per million persons exposed to 1 ng/m^3 over their lifetime;

2. more clearly acknowledge that the unit risk recommendation is based upon the staff's no-threshold policy rather than any scientifically conclusive determination; and

3. recommend the use of the DHS' "best" risk estimate rather than the use of the DHS' "upper bound" risk estimate.

We recommend that the ARB's Part A source assessment be revised to:

4. address ship, railroad, and airplane cadmium emissions which a California Energy Commission (CEC) staff report indicates may be about nine times higher than the corresponding stationary source emissions;

5. clarify in Tables III and III-1, and in the text on page III-6, that one category, industrial boilers, contributes 70 percent of the total residual fuel oil combustion emissions and 60 percent of the total oil combustion emissions identified; and

6. explain why the ARB estimate of industrial boiler residual fuel use is three times higher than the corresponding CEC staff estimate.

We cannot overemphasize the importance of revising Part B to include a scientifically objective presentation of the cadmium threshold alternative. As discussed more fully in Attachment A, we urge DHS to estimate the threshold below which there may be no risk, and to use this threshold alternative in their range of risk estimate. Attachment B contains excepts from the 1985 Environmental Protection Agency (EPA) Cadmium Update which illustrates how such a threshold model comparison could be more objectively presented. We also note that Southern California Edison raised this issue in their January 21, 1985 comments (see ARB Report, Part C, SCE, page 6, bottom paragraph).

We disagree with the DHS recommendation that the upper bound risk estimate, rather than DHS' own "best" risk estimate, be used to estimate risks. DHS' reasoning that the upper bound risk is more appropriate because it provides an extra safety factor to protect "sensitive" populations and to protect against risk of death from cancer at other sites has not been scientifically justified. No data are cited indicating the existence of more sensitive populations. Also, there are no data that indicate increased risks of deaths from cancer at other sites (see revisions to Part B, page 63). Please note that EPA concluded that the use of the upper bound risk would be "an unnecessary added level of conservatism" (see EPA, page 163 in Attachment B).

Our comments on Part A are detailed in Attachment C. The applicable portion of the CEC Report referenced is attached as Attachment D. Please call me at (415) 972-6901 or J. T. Holcombe at (415) 972-6910 if you have any questions about these comments.

Sincerely,

Attachments

ATTACHMENT A

PART B OF THE JUNE 1986 CADMIUM RISK ASSESSMENT SHOULD BE REVISED TO STATE THAT THERE MAY BE A THRESHOLD BELOW WHICH THERE IS NO RISK FROM EXPOSURE, AND THAT THE RANGE OF RISK IS ZERO TO 12 CASES PER MILLION PERSONS EXPOSED TO 1 ng/m^3

In its 1985 Cadmium Risk Assessment Update the United States Environmental Protection Agency (EPA) properly addressed the likelihood that there could be a threshold for cancer risks from cadmium exposures. EPA concluded that its simple threshold model adequately fit the data.[1] EPA further concluded that:

1. There is no solid scientific basis for any mathematical model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards;[2] and

2. An empirical threshold model that is also consistent with the observed data gives a unit risk estimate of zero[3] at typical ambient exposures.

In California, the Department of Health Services (DHS) is required to estimate "the range of risk to humans resulting from current or anticipated exposure".[4] We believe that refers to the full range of risk, which in this case should be stated as zero to 12 cases per million persons exposed to 1 ng/m^3 of cadmium. Although the DHS qualifies its estimate of 2-12 cases per million by stating that "the actual risk may lie in or below that range"[5], this is not sufficient since other experts have acknowledged that a zero risk estimate could be equally valid. Specifically, EPA has estimated that a constant lifetime exposure to 10 µg/m^3 cadmium would not cause any risk under the threshold

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1 Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, EPA-600/8-83-02 5F, June 1985 (final), page 159 attached.

2 EPA, page 138 attached.

3 EPA, page 8 attached.

4 Health and Safety Code Section 39660(c).

5 DHS Revisions to Part B, "Report to the Air Resources Board on Cadmium Submitted to the SRP for Review, page 4a.

model.[6] Since the highest average ambient concentration reported in the Part A Report was only 10.8 ng/m^3, the reported concentrations are a factor of one thousand below this plausible threshold, and a zero risk estimate is far more likely -- particularly since there is relatively little evidence that cadmium is particularly mutagenic even at high concentrations.

DHS seems to assert that since "the carcinogenic activity of cadmium may occur through a mechanism for which no threshold exposure level exists"[7] (emphasis added), there is no need to present an objective evaluation of the likelihood that it may not occur through such a mechanism. DHS should clearly acknowledge that there is no data establishing that threshold mechanisms could not predominate, and follow EPA's example and present an alternative threshold model which would best fit the data. DHS Tables I-7[8] and IX-6[9] should be expanded to include comparative risks at ambient concentrations under the alternate threshold assumption in a manner similar to that presented in EPA Table 26.[6] Similar comparisons should be included in DHS Table IX-2[10,11], Figure IX-1[12] and Figure I-1[13]. For clarity, the least squares fit data[14] should be tabulated in a manner similar to that shown in EPA Table 25[15]. Similarly, the DHS should follow the EPA Table 25 example on observed versus predicted data comparison by revising DHS Table IX-4[16] to also include a comparison with the incidence that would be predicted by the threshold model, not just with the incidence predicted by the linear no threshold model.

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6 EPA page 162 attached.

7 DHS Revisions to Part B, page 47.

8 DHS Revisions to Part B, page 6.

9 DHS Revisions to Part B, page 65.

10 DHS Part B (with revisions), page 84.

11 DHS Revisions to Part B, page 66.

12 DHS Part B (with revisions), page 85.

13 DHS Revisions to Part B, page 7.

14 DHS Revisions to Part B, page 62.

15 EPA, page 160 attached.

16 DHS Revisions to Part B, page 59.

If the DHS staff recommends a linear non-threshold upper bound range of risk estimate, any such recommendation should be clearly identified as being based on policy, not on a scientific determination. Furthermore, any such recommendations should only be made after DHS has objectively presented the full range of plausible alternative risk estimates -- including the EPA threshold model risk estimate. Risk managers need to know the relative likelihood of such a zero risk alternative so that they can consider the relative uncertainty of different upper bound risk assessments when faced with competing risk management alternatives.

ATTACHMENT B

EPA-600/8-83-025F
June 1985
Final

UPDATED MUTAGENICITY AND CARCINOGENICITY ASSESSMENT OF CADMIUM

Addendum to the Health Assessment Document for Cadmium
(May 1981) EPA-600/8-81-023

Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

Quantitative Assessment

Since humans are exposed to cadmium dust or fumes, and the rats used for study were exposed to cadmium chloride aerosol, a limitation inherent in the use of such studies for estimating human risk is the possible difference between humans and rats with regard to lung retention of particulates, or between the biological effectiveness of cadmium chloride aerosol administered to rats and the dust and fumes inhaled by workers. Since the data are not clear on this point, assumptions of equal lung uptake and equal effectiveness have been made herein for the purpose of arriving at an assessment of the human risks.

Given these assumptions, combined with other assumptions and conventions used in quantitative risk assessment procedures, the Takenaka et al. (1983) data on lung carcinomas in rats during lifetime inhalation exposures to cadmium chloride aerosol were analyzed. As a result of this analysis, the upper-bound incremental cancer risk to humans who continuously breathe 1 $\mu g/m^3$ of elemental cadmium for a lifetime is estimated to be 9.2×10^{-2}.

Based on respiratory cancer rates from the Thun et al. (1985) study of cadmium smelter workers, and using a linear model that is consistent with the data, the upper-bound incremental cancer risk from lifetime exposure to 1 $\mu g/m^3$ of cadmium in the air is estimated to be 1.8×10^{-3}.

The 95% confidence bound on this estimate, which takes into account only the statistical variability of the cancer rates, gives a range of 3.5×10^{-3} to 1.7×10^{-4}. However, this range does not account for possible deviations of the true (unknown) model from the linear model or of actual exposure from estimated exposure. For example, an empirical threshold model that is also consistent with the observed data gives a unit risk estimate of zero. Even with the uncertainties surrounding the estimate based on human data, it is felt that this

QUANTITATIVE ESTIMATION

INTRODUCTION

This quantitative section deals with the unit risk for cadmium in air and the potency of cadmium relative to other carcinogens that the Carcinogen Assessment Group (CAG) has evaluated. The unit risk estimate for an air pollutant is defined as the incremental lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 $\mu g/m^3$ of the agent in the air that they breathe. These calculations are done to estimate, in quantitative terms, the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: 1) to compare the carcinogenic potencies of several agents with each other, and 2) to give a crude indication of the population risk that would be associated with air or water exposure to these agents, if the actual exposures were known.

The data used for quantitative estimation are taken from one or both of the following: 1) lifetime animal studies, and 2) human studies where excess cancer risk has been associated with exposure to the agent. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, then response will also occur at all lower doses with an incidence determined by the extrapolation model.

<u>There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards.</u> For practical reasons, such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore,

An estimate of $\Delta^* = \Delta \times 10^6$ is obtained from the equation

$$10.99 = \frac{2.35}{3.77 + 1.18\ \Delta^*} + \frac{29.63}{4.61 + 4.23\ \Delta^*} + \frac{39.09}{2.50 + 5.58\ \Delta^*}$$

which has the solution $\Delta^* = 0.642$ so that $\Delta = 6.42 \times 10^{-7}$. The $V(\Delta)$ is estimated to be $V(\Delta) = 1.27 \times 10^{-13}$ so that $\sqrt{V(\Delta)} = 3.56 \times 10^{-7}$, and the 95% upper and 5% lower confidence bounds are approximately $\Delta_u = 12.26 \times 10^{-7}$ and $\Delta_\ell = 0.58 \times 10^{-7}$, respectively. It should be noted that this measure of variability only takes into account random sampling error. It does not account for potential error due to an assumed incorrect model or biased exposure estimates.

To show how a different assumed model could influence risk estimates, the following ad-hoc "threshold" model can be considered. This model is not based on any biological information. It simply uses the highest dose group with no observable statistically elevated risk as the threshold and assumes linearity in accumulated dose beyond that point. It is assumed that

$$h(t) = \begin{cases} 0 & X < 1754 \\ \Delta\ (X - 1754) & 1754 < X \end{cases}$$

where 1754, the guessed-at threshold, is the boundary point of the maximum exposed group in $\mu g/m^3$-years. For this model an estimate of Δ is

$$\Delta = (7 - 2.5) \div (2522 - 1754) \times 2214 = 2.65 \times 10^{-6}$$

In Table 25 the fit of each model is shown and evaluated using the X^2 goodness-of-fit test.

We note that <u>both the "threshold" and linear models give an adequate fit to the data.</u> As a result, arguments other than purely statistical must be used to select the appropriate model.

TABLE 25. GOODNESS-OF-FIT MODELS FITTED TO THE THUN DATA

Exposure interval $\mu g/m^3$-years midpoint	Number of cases expected under linear model using as the estimate of parameter Δ the			Expected number of cases under threshold model	Observed
	Lower bound	MLE	Upper bound	$\Delta = 2.65 \times 10^{-6}$ if $X > 1754$ $\Delta = 0$ if $X < 1754$	
< 350 (168)	3.84	4.53	5.21	3.77	2
351-1754 (727)	4.85	7.33	9.80	4.61	7
> 1754 (2522)	2.82	6.08	9.34	7.00	7
	X^2 goodness-of-fit statistic				
	7.971	1.567	3.364	2.070	

SOURCE: Thun, letter of April 10, 1984; Thun et al., 1985.

TABLE 26. ESTIMATED RISKS FOR VARIOUS MODELS BASED ON THUN DATA

Model used	Risk due to a constant lifetime exposure of 1 $\mu g/m^3$	10 $\mu g/m^3$	100 $\mu g/m^3$
Linear nonthreshold			
Upper bound	3.5×10^{-3}	3.4×10^{-2}	2.9×10^{-1}
MLE	1.8×10^{-3}	1.8×10^{-2}	1.7×10^{-1}
Lower bound	1.7×10^{-4}	1.7×10^{-3}	1.6×10^{-2}
Threshold model	0.0	0.0	3.7×10^{-1}
April 1984 model[a]	1.9×10^{-3}	1.9×10^{-2}	1.7×10^{-1}

[a]Used in the External Review Draft of the Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, prepared by the Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, April 1984.

SOURCES: Thun, letter of April 10, 1984; Thun et al., 1985.

unit risk estimate of 1.8×10^{-3}. A higher estimate of 3.5×10^{-3} would be obtained if the 95% upper bound of the parameter were used. However, it is felt that this is an unnecessary added level of conservatism, since the model used already inflates the risk estimate if nonlinear components exist or confounding factors are present.

The unit risk estimate based on the animal bioassay, 9.2×10^{-2}, also gives a higher estimate. However, species differences and cadmium form differences make an estimate from this source intrinsically less reliable than the one derived from the assumed human exposures. In addition, it must be kept in mind that these are upper-bound estimates. The true unit risk could range from this upper bound to a very small value approaching zero.

RELATIVE POTENCY

One of the uses of the concept of unit risk is to compare the relative potencies of carcinogens. For the purposes of the present analysis, potency is defined as the linear portion of the dose-response curve, and is used to calculate the required unit risk factors. In this section, the potency of cadmium is compared with that of other chemicals that the CAG has evaluated as suspect carcinogens. To estimate the relative potency on a per mole basis, the unit risk slope factor is multiplied by the molecular weight and the resulting number, expressed in terms of $(mmol/kg/day)^{-1}$, is called the relative potency index.

Figure 2 is a histogram representing the frequency distribution of relative potency indices for 54 chemicals that have been evaluated by the CAG as suspect carcinogens. The actual data summarized by the histogram are presented in Table 27. Where human data have been available for a compound, such data have been used to calculate these indices. Where no human data have been

ATTACHMENT C

PART A OF THE JUNE 1986 CADMIUM RISK ASSESSMENT SHOULD BE REVISED TO INCLUDE BUNKER C FUEL OIL USE BY SHIPS, AND TO DISTINGUISH BETWEEN INDUSTRIAL STEAM GENERATOR FUEL USE AND OTHER FUEL USE CATEGORIES

The California Energy Commission (CEC) March 14, 1986 staff draft Biennial Fuels Report lists in Table A-2, page A-4 of that report, fuel deliveries by category through 1984. Converting their data, expressed as trillion BTUs, into million gallons of oil[1] yields the following:

Fuel Oil Deliveries by End User Category	Residual Only 1983	Residual Only 1984	Residual and Other[2] 1983	Residual and Other[2] 1984
Electric Utility	439	148	439	148
Residential	0	0	0	0
Commercial	134	134	134	134
Industrial	309	309	4,610	4,939
Transportation	2,258	2,923	2,923	2,923

PGandE recommends that the utility fuel use in Appendix C of the ARB's Part A Cadmium Report be revised to reflect the 1984 data. That data, which indicates emissions decreased by a factor of 3, appears more representative of current fuel use projections.

PGandE notes that the ARB estimate of industrial boiler residual fuel use in Appendix C is roughly three times the corresponding CEC estimate for all industrial residual fuel oil deliveries. That difference should be explained. If it reflects the inclusion of oil field steam generator combustion of heavy crude, PGandE recommends that such heavy crude emissions be separately calculated and listed. The heavy crude generally used in such steam generators is likely to be far higher in sulfur and heavy metal content than the corresponding low sulfur residual fuels more typically used by other industries. Also, it is likely that such emissions will either substantially decrease if current oil prices prevail, or will be replaced by natural gas fueled cogeneration projects if oil prices return to previous highs.

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1 Assuming 42 gallons/6.25 million BTU.

2 "Other" is other than motor gasoline, distillate, and residual and presumably includes both crude combustion and feedstock use.

Given that the CEC identifies nine times as much residual fuel oil use in the ship and rail transportation sector as in the industrial sector, and the ARB identifies industrial boilers' use of residual fuel oil as the second largest source of cadmium emission in the state, the report should be revised to include ship and railroad use of Bunker C fuel oil. The report should also consider aviation fuel use, which the CEC estimated was 2,634 million gallons in 1984.

PGandE recommends that ARB Tables III (page 14) and III-1 (page III-5) be revised to more accurately reflect the data in Appendix C. As detailed in Appendix C, industrial boiler residual fuel use contributes more than 70 percent of total residual fuel emissions and more than 60 percent of total oil combustion emissions. Yet no mention of this appears in either table or in the descriptive paragraph on page III-6. PGandE recommends that Table III be revised to replace the oil, coal, and motor vehicle categories with the following: industrial steam generators; other stationary source fuel combustion; motor vehicle fuel combustion; and other mobile source fuel combustion. In Table III-1, the "industrial steam generator" category should be subdivided into its primary contributors, presumably low sulfur fuel oil boilers and high sulfur oil field steam generators. Similarly, the "other mobile source" category should be subdivided in Table III-1 into ship, rail, and aviation fuel related emissions. The other categories: utility residual fuel, commercial residual fuel, distillate fuel oil, coal, waste oil, and sludge incineration are comparatively insignificant. Nevertheless, we recommend also listing each such category in Table III-1 to give the public a better perspective of the relatively low levels of such emissions.

In 1984, PGandE sampled cadmium concentrations in ten fuel oil tanks at six different PGandE power plant sites. Concentrations in three tanks were below the initial detection limit of 0.5 ppm. Concentrations in the remaining eight tanks averaged 0.39 ppm, with none measured higher than 0.52 ppm or lower than 0.31 ppm. This data is consistent with the 0.38 ppm data previously submitted by Southern California Edison. PGandE therefore recommends that the ARB not continue to imply that concentrations ranging as high as 5.1 ppm would be equally likely.

Since utility emissions are insignificant even at 5.1 ppm, and since similar ranges are not calculated for industrial boiler residual fuel use where the variety of source emission controls and permissible sulfur content is far higher and suggestive of far greater variations in cadmium emissions, PGandE recommends that only the 0.38 ppm utility estimate be reflected in Table III and III-1.

ATTACHMENT D

Biennial Fuels Report

CALIFORNIA ENERGY COMMISSION

March 14, 1986

DRAFT

TABLE A-2

HISTORICAL
DELIVERIES BY SECTOR
(Trillions of Btu)

SECTOR/ENERGY TYPE	1976	1977	1978	1979	1980	1981	1982	1983	1984
Electric Utility									
Natural Gas(22)	302	364	312	458	534	678	571	486	599
Petroleum									
Distillate(24)	0	0	0	0	0	0	2	2	2
Residual(25)	596	774	619	640	391	284	99	65	22
Subtotal	596	774	619	640	391	284	101	67	24
Coal(26)	135	141	110	138	152	165	187	188	182
Hydropower(27)	210	109	237	191	264	253	384	448	451
Nuclear(11)	51	87	81	96	51	36	37	43	138
Geothermal and Other(12)	74	74	60	80	101	113	91	130	134
Total	1,368	1,549	1,419	1,603	1,493	1,529	1,371	1,362	1,528
Electricity Delivered(28)	520	527	545	567	566	591	578	584	611
Conversion Loss	800	976	821	983	870	893	754	704	797
Transmission Loss(29)	48	46	53	53	57	45	39	74	120
Total Loss	848	1,022	874	1,036	927	938	793	778	917
Residential End User									
Electricity(30)	154	162	174	182	176	183	179	187	200
Natural Gas(31)	610	569	584	621	557	518	559	515	502
Petroleum(35)									
Distillate Fuel Oil	5	7	7	7	1	1	1	1	1
Subtotal Petroleum	5	7	7	7	1	1	1	1	1
LPG(37)	9	9	14	18	18	16	16	15	15
Subtotal Residential	777	747	779	828	752	718	755	718	718
Commercial End User									
Electricity(30)	194	187	191	198	204	197	197	201	213
Natural Gas(31)	183	187	174	177	165	178	187	173	172
Petroleum(35)									
Motor Gasoline	11	13	16	14	10	8	8	8	8
Distillate Fuel Oil	9	13	13	10	21	30	29	27	27
Residual Fuel Oil	25	27	25	28	43	40	35	20	20
Subtotal Petroleum	45	53	54	52	74	78	72	55	55
LPG(37)	2	2	3	3	3	3	3	3	3
Subtotal Commercial	424	429	422	430	446	456	459	434	443
Industrial End User									
Electricity(30)	172	178	180	187	186	211	202	191	198
Natural Gas(31)	747	693	674	769	728	682	609	513	562
Petroleum(35)									
Motor Gasoline	8	6	5	6	9	7	7	7	7
Distillate Fuel Oil	78	104	110	138	105	112	127	103	103
Residual Fuel Oil	106	107	90	89	85	59	55	46	46
Other Petroleum	544	561	756	711	681	784	569	640	689
Subtotal Petroleum	736	778	961	944	880	962	758	796	845
LPG(37)	54	47	47	41	39	39	35	27	37
Coal(26)	57	66	60	60	69	72	65	26	26
Subtotal Industrial	1,766	1,762	1,922	2,001	1,902	1,966	1,669	1,556	1,658
Transportation End User									
Petroleum(35)									
Motor Gasoline	1,288	1,378	1,384	1,427	1,353	1,306	1,325	1,400	1,400
Aviation Fuels	336	372	387	381	363	348	335	357	392
Distillate Fuel Oil	211	257	280	249	259	281	252	331	356
Residual Fuel Oil	188	236	289	324	410	385	330	336	435
Lube Oil	1	1	1	2	2	3	3	3	2
Subtotal Petroleum	2,025	2,244	2,351	2,383	2,387	2,323	2,245	2,427	2,585
LPG(37)	1	1	1	2	2	3	3	3	3
Subtotal Transportation	2,026	2,245	2,352	2,385	2,389	2,326	2,248	2,430	2,588
Total End User	4,993	5,183	5,465	5,644	5,489	5,466	5,131	5,138	5,407

TOTAL END USER DELIVERIES

End User Deliveries									
Electricity	520	527	545	567	566	591	578	584	611
Natural Gas	1,540	1,449	1,432	1,567	1,450	1,378	1,365	1,201	1,226
Petroleum(34)									
Motor Gasoline	1,307	1,397	1,405	1,447	1,372	1,321	1,340	1,415	1,415
Aviation Fuels	336	372	387	381	363	348	335	357	392
Distillate Fuels	303	381	410	404	386	424	409	462	487
Residual Fuels	319	370	404	441	538	514	420	402	501
Misc. Fuels	545	563	757	713	683	757	572	643	691
Subtotal Petroleum	2,810	3,083	3,363	3,386	3,342	3,364	3,076	3,279	3,486
Liquified Petroleum Gas	66	58	65	64	62	61	57	48	58
Coal	57	66	60	60	69	72	65	26	26
Total End User	4,993	5,183	5,465	5,644	5,489	5,466	5,131	5,138	5,407

Western Oil and Gas Association
727 West Seventh Street, Los Angeles, California 90017
(213) 627-4866

August 19, 1986

Members of the Board
California Air Resources Board
1102 "Q" Street
Sacramento, CA. 95812

Subject: Comments of the Western Oil and Gas Association on Draft Report to the Air Resources Board on Cadmium

Dear Board Members:

Once again Western Oil and Gas Association (WOGA) appreciates the opportunity to comment on the risk assessment procedure as applied by the Air Resources Board (ARB) to control ambient air concentrations of hazardous materials in California. The thrust of the following comments is directed to the draft cadmium document. There is much to support in the work. However, the final range is too small to describe precisely the inherent uncertainties in the risk estimate. Further, the degree of uncertainty in the cadmium risk assessment is minimized by mathematical manipulation which may be unjustified (i.e., DHS recalculated animal data disregarding conversions for differences in metabolic rate). In addition, it appears to WOGA that the Department of Health Services (DHS) has not been consistent in its approach to utilizing available human data for risk assessment. In some cases (e.g., benzene) animal data were used when valid human data were available and in other instances (e.g., cadmium) the reverse is true.

In regard to the cadmium draft report, we wholeheartedly concur with the use of human over animal data. Our experience has consistently found the human experience to be more valuable in predicting actual human risk. As DHS states in the cadmium document, the possible roles of chance, bias, and/or confounding variables, in distorting the true dose response relationship in the occupational study, were likely to be small. The net direction of these potential errors was more likely to result in an overestimate of substance potency. Thus, we believe as does DHS that use of the epidemiologic data in quantitative risk assessment is appropriate.

Two assumptions lead to a confidence in the calculated risk for cadmium that may be unwarranted. Although we agree that a range of risk is proper, in the case of cadmium the upper bound risk expressed by DHS (2×10^{-6} to 12×10^{-6} per ng/m^3) is too small a range to be useful and could mislead the risk manager by assigning more confidence than perhaps should be given to the estimation. Many critical assumptions affect this range, e.g., the extrapolation model, exposure assumptions, chemical speciation. In view of the fact that EPA concluded a simple threshold model would adequately fit the data, zero would be appropriate for a lower range. Clearly, a broader range would more appropriately describe the breadth of uncertainty we all agree exists. Further, the recalculation of the animal data, disregarding conversions for metabolic rate, has given

figures which are very close to the upper bound risk predicted by the epidemiology. This congruence may be coincidental and DHS's use of this data to lend additional support to the risk predicted from the human data is inappropriate. Given the large number of viable assumptions, myriad possibilities could be supported with some manipulation of the data.

Our review of the draft risk assessment for cadmium has suggested inconsistencies in DHS's use of human epidemiology for risk assessment. In contrast to the approach taken for cadmium, the benzene risk assessment was calculated from animal data although human data was available. This was apparently justified by the fact that it is common practice to use the 95% confidence limit based on the most sensitive site and species. WOGA believes the cadmium approach applies equally to the benzene database. We do not believe that animal studies are more than a surrogate for adequate epidemiology. Thus, valid epidemiological studies are the best source of data, eliminating the inherent uncertainty in extrapolating from animals to humans. The inconsistency of the approaches is perplexing in that DHS argues first for utilization of animal data (benzene) and then for employment of human data (cadmium).

The upper bound risk for benzene was derived from data on the most sensitive site in animals, the preputial gland in mice, a site which has no human analogue. More appropriate data might have been the epidemiology which DHS used to derive the lower bound risk calculation. Again, as DHS concludes in the cadmium risk assessment, even the use of the epidemiology data is likely to result in an overestimation of risk.

To conclude, WOGA urges ARB and DHS to:

- Be consistent in the approach and assumptions which underlie risk assessment for each chemical considered;
- Use human over animal data when available;
- Communicate the uncertainty inherent in the estimation of risk; and
- Avoid statements which unjustifiably diminish the uncertainty as this is misleading to the risk manager and may cause misappropriation of limited resources.

Sincerely yours,

Robert Harrison

Robert Harrison
Vice President and
General Manager

RH:va
cc: Mr. Bill Loscutoff, ARB
Chief, Toxic Pollutants Branch

AIR RESOURCES BOARD STAFF RESPONSES TO PUBLIC COMMENTS ON THE JANUARY 1986 DRAFT REPORT

Comment: Southern California Edison (SCE) claims that, in deriving an emission factor for utility boilers burning fuel (residual) oil, the ARB took the average of the highest identified emission rate from the Taback Study and the estimate from the Krishnan Study which applies to utility boilers with an electrostatic precipitator (ESP) control device.

Response: The ARB emission factor for utility boilers was based on all five tests reported in the Taback Study. Staff noted that SCE did not list data from one of these tests (#24) in its analysis. Although California utility boilers are not equipped with ESPs, Taback et. al. concluded that the ESP is a better control device for utility boilers than fabric filters (baghouses) or scrubbers. Therefore, ARB staff believes the emission factor was reasonably derived, and represented the best estimate based on available data. Because ESPs are not used by California utilities, and other control devices are less efficient (according to Taback), staff believes that use of tests from ESP-equipped utility boilers would, if anything, understate cadmium emissions.

Comment: SCE points out that the cadmium content of crude and fuel (residual) oils varies widely, and therefore data which are most representative of California power plants should be used to estimate emissions. SCE states that the average measured cadmium concentrations in fuel oil at two SCE power plants is 0.1 ppm.

Response: ARB staff agree that there may be variation in trace element concentrations in fuel oils; to reflect this, ARB staff has revised the report to include a range of emissions. Data provided by SCE subsequent to the issuance of the draft Report on Cadmium (December 1985) indicates that concentrations below 0.01 ppm have been measured in fuel oils at SCE power plants. This information was used to develop a low emission factor of $8.3\ 10^{-8}$ lb Cd/gallon oil. A high emission factor of $5.1\ 10^{-6}$ lb Cd/gal oil was calculated from the Krishnan Study. Using these emission factors, emissions from utility boilers were estimated to range between 0.02 and 1.1 tons year. This range brackets emissions calculated from the 0.1 ppm average cadmium in fuel oil reported by SCE.

Comment: The Cadmium Council, Inc. argues that airborne exposure to cadmium is minimal, and that this is a reason not to list cadmium as a toxic air contaminant.

Response: Review of data on atmospheric cadmium concentrations in the State shows that the average population exposure ranges between 1 and 2.5 ng/m^3 (for 21 million people), with long-term exposure near three large sources predicted to be 40 ng/m^3 (for 57,000 people). Using DHS recommended dose-response values, the resulting excess lifetime cancer risk is from 2 to 30 per million for a large number of Californians, and a worst-case excess lifetime cancer risk is 80 to 480 per million for almost 60,000 people living close to sources.

Comment: CalMat Co. pointed out that our estimates of 1981 California cement production were high by a factor of 3.7.

Response: ARB acknowledges this error and has corrected it; data on California cement production for 1984 have been used in the revised report (Part A, p. III-6, and Appendix C to Part A, p. C-4).

Comment: CalMat Co. pointed out that approximately 1.6 tons of feed material to the rotary kiln are needed to produce one ton of clinker (not cement, as stated in the report).

Response: According to the Bureau of Mines of the United States Department of the Interior (1), "About 1.8 tons of raw material are required to manufacture 1 ton of finished cement; 1.7 tons are used to make clinker, and the remaining 0.1 ton is added during the clinker-grinding process." Two other references (2, 3) reported a ratio of 1.6 to 1.0 for raw material to cement. ARB staff were aware of the different ratios reported by these references and chose to use a conservative estimate of 1.6 tons of raw material to 1.0 ton of cement.

Comment: CalMat Co. suggested that cadmium emissions from cement manufacturing could be estimated using data on particulate matter emissions from the rotary kilns used to produce clinker. CalMat Co. based their estimate on:

1. statewide cement production of 7.88 million tons (1981);
2. clinker production (approximately 95% of cement production) of 7.72 million tons;

3. a ratio of 1.6 tons kiln feed material to ton of clinker produced, yielding an estimate of 12.4 million tons kiln feed;
4. the assumption that all rotary kilns in California are equipped with fabric filter baghouses or electrostatic precipitators meeting Federal (EPA) New Source Performance Standards of 0.3 lb. particle emissions from the kiln per ton of kiln feed, giving an estimate of 3.71 million tons of emitted particulate;
5. a mean concentration of 21 ppm (by weight) cadmium in baghouse catch dust, which was assumed to be representative of emitted particulate matter. On this basis, CalMat Co. estimated cadmium emissions from rotary kilns to be 0.039 ton/year.

Response: ARB staff agrees with CalMat Co. that cadmium emissions from cement manufacturing can be estimated using estimated particulate matter (PM) emissions. However, CalMat Co. appears to have considered only estimated PM emissions from rotary kilns and has excluded emissions from other parts of the overall cement manufacturing process. Attached is a copy of the flow diagram of the Portland cement manufacturing process from the "Compilation of Air Pollutant Emission Factors", Fourth Edition (3). As seen in the diagram, the cement manufacturing process includes 1) quarrying and crushing, 2) raw material storage, 3) grinding and blending, 4) finish grinding, and 5) packaging. These processes are also potential sources of PM emissions. Normally, the emissions from quarrying, crushing, and raw material storage are not controlled.

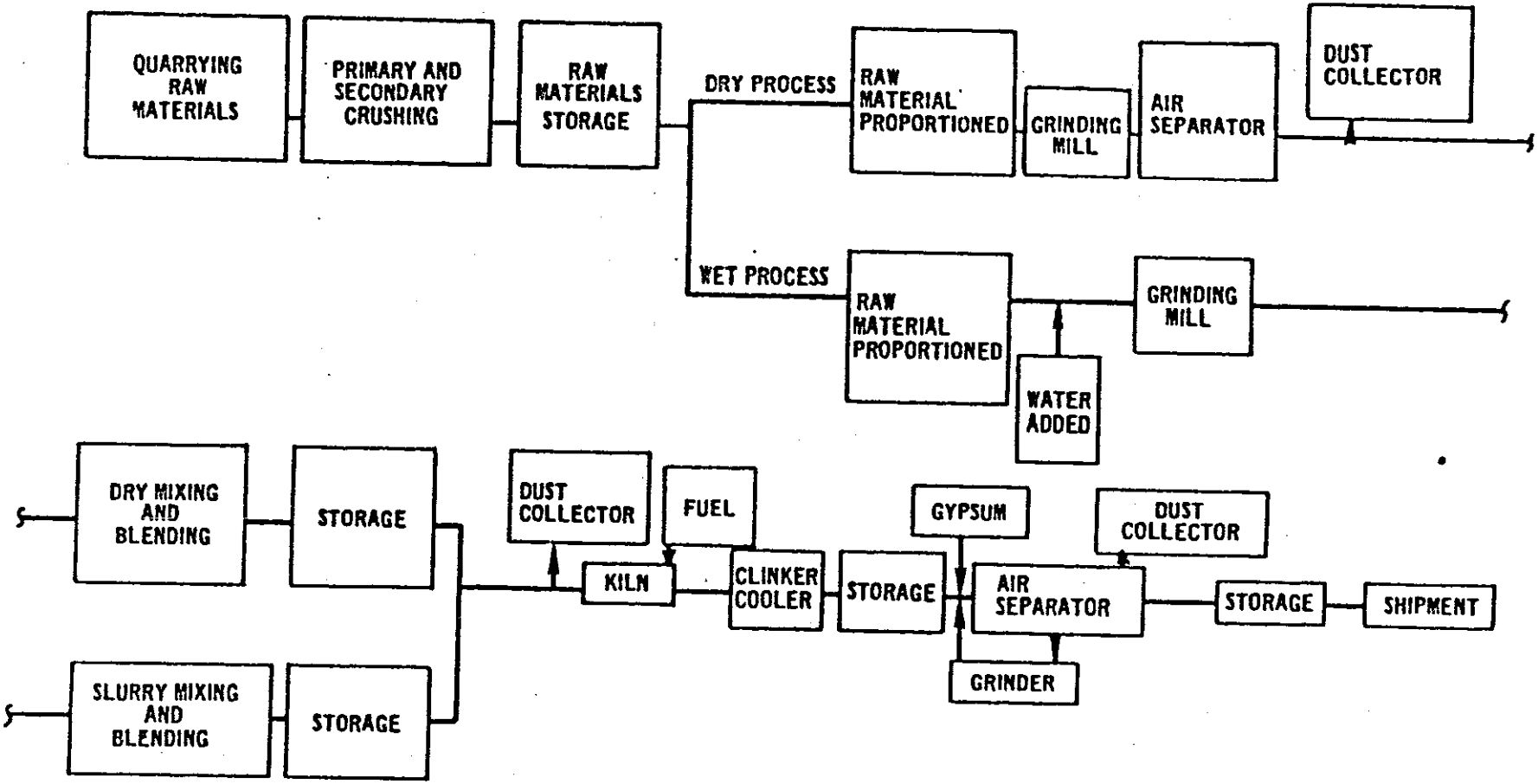

Figure 8.6-1. Basic flow diagram of portland cement manufacturing process.

In 1984, California cement manufacturing plants produced 8.72 million tons of cement (4) and emitted approximately 3,030 tons of PM (5) excluding PM emissions from fuel.

Assuming the cadmium concentration in the cement kiln dust removed from the rotary kiln baghouse or ESP equals the cadmium concentration in the particulate matter, cadmium emissions from cement manufacturing can be estimated from total PM emissions and the cadmium concentration in cement kiln dust.

The cadmium concentration in cement kiln dust from 9 California cement plants ranged from 5 ppm to 352 ppm and averaged 79 ppm (6,7). Using these data and the total PM emissions, the 1984 cadmium emissions from California cement plants are estimated to be:

Lower Estimate	Upper Estimate	Estimate based on mean Cd concentration
(TPY)	(TPY)	(TPY)
0.015	1.1	0.24

We have listed this range of 0.02 to 1.1 tons/year as cadmium emissions from cement manufacturing (see Overview, p. 14, Part A, p. III-5, and Appendix C, p. C-4).

Comment: PG&E recommends that the fuel use in Appendix C of the ARB's Part A Cadmium Report be revised to reflect 1984 data.

Response: 1984 data were not available at the time the original cadmium emission estimate for residual oil combustion was made. We have updated the estimate to reflect 1984 data.

Comment: "PG&E notes that the ARB estimate of industrial boiler residual fuel use in Appendix C is roughly three times the corresponding CEC estimate for all industrial residual fuel oil deliveries. That difference should be explained. If it reflects the inclusion of oil field steam generator combustion of heavy crude, PG&E recommends that such heavy crude emissions be separately calculated and listed. The heavy crude generally used in such steam generators is likely to be far higher in sulfur and heavy metal content than the corresponding low sulfur residual fuels more typically used by other industries. Also, it is likely that such emissions will either substantially decrease if current oil prices prevail, or will be replaced by natural gas fueled cogeneration projects if oil prices return to previous highs."

Response: Crude oil burned in boilers or steam generators at the oil fields may be included under residual fuel oil in the staff estimate. The emission data system (EDS) showed approximately 1.13 billion gallons of oil burned in the industrial category. Of this, aproximately 80 percent is burned for oil and gas production

activities (8). However, the data used did not differentiate between residual or crude oil. Therefore, we cannot separately estimate cadmium emission from residual or heavy crude oil combustion for this category. However, we agree with PG&E that heavy crude oil burned at oil field generators is higher in sulfur and metal content comparing to oil typically used by other industries. Thus, if crude oil is used, cadmium emissions from oil combustion may be underestimated.

There is uncertainty about future fuel use. We do not have an adequate basis to assume a substantial decrease in cadmium emissions from residual oil combustion for the industrial category as suggested by PG&E.

Comment: a) "Given that the CEC identifies nine times as much residual fuel oil use in the ship and rail transportation sector as in the industrial sector, and the ARB identifies industrial boilers' use of residual fuel oil as the second largest source of cadmium emission in the state, the report should be revised to include ship and railroad use of Bunker C fuel oil. b) The report should also consider aviation fuel use, which the CEC estimated was 2,634 million gallons in 1984."

Response: a) Even though CEC reports that the residual fuel oil used by the transportation sector is approximately nine times higher than that for the industrial sector (9), we have not been able to document the use of such a large amount of fuel use in California. We suspect that much of it is used by ships outside coastal waters.

Of the amount of residual fuel oil reported by CEC in the transportation sector, we have only been able to document about 2 percent in California (9,10). In the revised cadmium report, cadmium emissions will also be estimated for ships and trains under residual and diesel combustion categories, respectively. However, these emissions will not be separately listed.

b) We are aware of the fact that cadmium emissions would also result from aviation fuel combustion; however, we have no data to estimate cadmium emissions for this category.

Comment: "PG&E recommends that ARB Tables III (page 14) and III-1 (page III-5) be revised to more accurately reflect the data in Appendix C. As detailed in Appendix C, industrial boiler residual fuel use contributes more than 70 percent of total residual fuel emissions and more than 60 percent of total oil combustion emissions. Yet no mention of this appears in either table or in the descriptive paragraph on page III-6. PG&E recommends that Table III be revised to replace the oil, coal and motor vehicle categories with the following: industrial steam generators; other stationary source fuel combustion; motor vehicle fuel combustion; and other mobile source fuel combustion. In Table III-1, the "industrial steam generator" category should be subdivided into its primary contributors, presumably low sulfur fuel oil boilers and higher sulfur oil field steam generators. Simiarly, the "other mobile source" category should be subdivided in Table III-1 into ship, rail, and aviation fuel related emissions. The other

categories: utility residual fuel, commercial residual fuel, distillate fuel oil, coal, waste oil, and sludge incineration are comparatively insignificant. Nevertheless, we recommend also listing each such category in Table III-1 to give the public a better perspective of the relatively low levels of such emissions."

Response: Table III and III-1 of the cadmium report will be revised and the cadmium emissions from utilities will be mentioned. We do not believe it is necessary to greatly expand the detail in Table III-1 at this time as suggested by PG&E. Should airborne cadmium be listed as a toxic air contaminant, emission estimates for cadmium will be refined and detailed to support risk management activities.

Comment: a) "In 1984, PG&E sampled cadmium concentrations in ten fuel oil tanks at six different PG&E power plant sites. Concentrations in three tanks were below the initial detection limit of 0.5 ppm. Concentrations in the remaining eight tanks averaged 0.39 ppm, with none measured higher than 0.52 ppm or lower than 0.31 ppm. This data is consistent with the 0.38 ppm data previously submitted by Southern California Edison. b) PG&E therefore recommends that the ARB not continue to imply that concentrations ranging as high as 5.1 ppm would be equally likely."

Response: a) We appreciate PG&E providing information on the cadmium concentrations of residual oil used at its plants. These data will be considered in estimating cadmium emissions from residual oil combustion.

b) A factor of 5.1 ppm was not used to develop the high estimate for utility boilers. The factor used previously was 5.1 lbs Cd per million gallons of oil burned. New estimates based on a factor of 0.52 ppm have been developed.

REFERENCES - PART C

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2. Taback, H.J., et al., 1979. Fine Particle Emissions from Stationary and Miscellaneous Sources in the South Coast Air Basin, KVB, Inc., for California Air Resources Board, Sacramento, CA.

3. United States Environmental Protection Agency (U.S. EPA), 1985. Compilation of Air Pollutant Emission Factors, Vol. 1: Stationary Point and Area Sources, Fourth Edition, Office of Air Quality and Planning Standards, Research Triangle Park, NC.

4. U.S. DOI, 1985. Mineral Industry Surveys, Cement in 1984. August 28, 1985. U.S. DOI, Bureau of Mines, Washington, DC.

5. California Air Resources Board (CARB), 1985a. Data retrieved from EDS, data base year 1984, on 3/5/1986. Emission Inventory Branch, Technical Support Division, Sacramento, CA.

6. Haynes, B.W. and G. Kramer, 1982. Characterization of U.S. Cement Kiln Dust, report IC 8885, U.S. DOI, Bureau of Mines, Maryland.

7. CARB, 1985b. Personal communication between Benjamin Haynes of U.S. DOI (Tel. (301) 436-7564) and Chris Nguyen of CARB on 2/28/86 regarding the identification of California cement kiln dust used in the "Characterization of U.S. Cement Kiln Dust" report.

8. CARB, 1986a. Data retrieved from the Emission Data System (EDS), inventory year 1984, run date 9-9-86. ARREPORT JOB 8643. Emission Inventory Branch, Technical Support Division, Sacramento, CA.

9. CEC, 1986. Biennial Fuels Report. Fossil Fuels Assessment Office, Assessments Division, California Energy Commission, Sacramento, CA.

10. CARB, 1986b. Data retrieved from EDS, inventory year 1983, run date 9-13-86. ARREPORT JOB 1954. Emission Inventory Branch, Technical Support Division, Sacramento, CA.

Department of Health Services

Staff Responses to Comments from the

Scientific Review Panel

(January 1986 Draft)

Comment:

The SRP stated that the DHS did not appear to have a policy for determining when to use animal data and when to use human data in a risk assessment.

Response:

The policy of the DHS staff has been to use the best evidence available for the risk assessment. The choice of human or animal data has been made on a case-by-case basis.

Human data are clearly preferable where studies are well designed and exposure is well documented, since this eliminates the uncertainty arising from interspecies extrapolation. Frequently, human exposure has not been well documented. In addition, information about potential confounding variables is often lacking.

On the other hand, in some cases the animal data may not be suitable. For example, in the animal data for asbestos, exposures were reported on mass basis instead of by fiber count. Since fiber count is the significant factor used in evaluating human health effects of asbestos, the DHS staff chose to use the human data.

Cadmium was the first chemical encountered in the AB 1807 process for which there was both a suitable animal study and a well designed human study with documented exposure estimates for individual workers and a positive

dose-response. This made it possible for the DHS staff to conduct two separate risk assessments.

Comment:

The SRP stated that DHS staff did not make clear the rationale for choosing to use the human-based risk assessment for cadmium.

Response:

As noted in the original report, the two risk assessments led to ranges of estimated risk that did not overlap. Using a more refined model to determine risk, the updated human-based assessment yielded a risk estimate about ten- to sixty-fold smaller than the animal-based assessment. In this instance, DHS staff chose to recommend the use of the human-based risk estimates even though these were smaller than the animal-based ones because:

(a) the use of a linear model with a correction for the healthy worker effect was judged to be sufficiently health-conservative,

(b) the amount of error in the measures of dose and effect from the Thun study were probably not large,

(c) the net direction of these errors was likely to result in an overestimate of cadmium's carcinogenic potency.

To further clarify our reasons for adopting the human-based risk assessment we have expanded the description of the study by Thun et al. and the discussion of the potential roles of confounding, bias and chance in explaining the findings of this study. (Section VII.J.2 Human studies, Respiratory cancer-Thun study.)

Comment:

DHS staff found the evidence of carcinogenicity in humans to be sufficient, but did not state the grounds for this interpretation of the

evidence, nor the reasons why this conclusion differed from that of the IARC and the EPA.

Response:

Although the IARC has developed specific criteria for evaluating the evidence for human carcinogenicity as sufficient, limited or inadequate, the study by Thun et al. was not available to that agency when they last evaluated cadmium. Based on the evidence available at that time on prostate cancer, IARC (1982) concluded that there was limited evidence for carcinogenicity in humans. Based on the Thun study, the Environmental Protection Agency (EPA, 1985) also classified the evidence as limited. While they considered the Thun study to be very strong evidence of human carcinogenicity, the lack of another well-conducted study which confirmed these results influenced their decision not to classify the evidence as sufficient. For the purpose of risk assessment, it is unnecessary for the DHS to make such a judgment because cadmium is clearly an animal carcinogen. Since the IARC, the EPA and the DHS consider animal carcinogens to be potential human carcinogens, cadmium is a candidate for a quantitative risk assessment. The document has been revised to reflect this.

Comment:

The SRP questioned the recommendation of the DHS staff to use the human-based risk assessment when the EPA found the animal evidence adequate for use in risk assessment.

Response:

The DHS also found the animal evidence adequate for use in risk assessment. Both EPA and DHS performed two risk assessments, one based on animal data and one based on human data. EPA also chose to recommend their

human-based risk estimate rather than their animal-based estimate, stating "species differences and cadmium form differences make an estimate from this source (animal) intrinsically less reliable than the one derived from the assumed human exposures" (EPA, June 1985). Though their choice of model for the human-based risk estimation differed from the one used by the staff of DHS, the final estimates were quite close.

Comment:

The model used by the DHS for quantitative risk estimation may not have been the best choice, particularly since it did not accomodate all of the data.

Response:

DHS staff has revised the risk assessment by fitting a more appropriate model which accomodates all of the data. This model regresses the observed deaths as a function of two factors: the cumulative dose and the expected deaths. This function has two parameters: one for the carcinogenic potency of the cumulative dose, and the other for the observed "healthy worker effect." Since the low exposure group experienced a marked deficit of lung cancer deaths, these workers can be inferred to represent a healthier group than the general population of white males of the same ages. By estimating the degree to which the cohort under study differs from the population, this model separates the effect of dose from the countervailing healthy worker effect. In particular, it ensures a more health-conservative estimate of carcinogenic potency.

Comment:

The SRP wished to see the range for extrapolation between the observed data and the ambient levels in California.

Response:

The workers were exposed to cumulative doses which were equivalent to a constant 24-hour/day lifetime exposure of concentrations of 2.7, 11.8 and 41.0 $\mu g/m^3$. Ambient air in California is estimated to contain concentrations of 1 to 2.5 ng/m^3. Thus using the daily dose rate, the range of extrapolation is 10^{-3}, (three orders of magnitude) or a thousandfold. The median cumulative exposures for the workers were 184, 796 and 2762 mg-days/m^3 while the population in California would be expected to receive on average, over an 80-year lifespan, .029 to .073 mg-days/m^3 . (1 ng X 365 days X 80 years = 29200 ng-days/m^3 = .029 mg-days/m^3.) Thus using lifetime cumulative dose, the range of extrapolation is 3-4 orders of magnitude. In some hot spots, California residents would be expected to receive 1.17 mg-days/m^3 representing exposures 2 - 3 orders of magnitude lower than the workers' exposures. The range of extrapolation has been included in the revised Executive Summary of Part B of the document.

Department of Health Services

Staff Responses to Public Comments

(January 1986 Draft)

Comment:

Ciba-Geigy objected to the use of occupational exposures for extrapolating risks at ambient levels of cadmium, which are several orders of magnitude lower. They argued that (a) cadmium levels declined over time, (b) workers were also exposed to arsenic, lead and zinc, (c) urine levels indicated high exposures, which may have been the result of poor hygiene practices, (d) "smoking could have accounted for half the increase," and (e) smoking habits were determined retrospectively.

Response:

The uncertainty involved in extrapolating to very low ambient levels is acknowledged by DHS staff. However, it is not feasible to directly observe the carcinogenic effect of low-level chemical exposures. The only quantitative data on cadmium's carcinogenicity are (1) experimental animal data involving daily exposures close to the OSHA permissable exposure level, and (2) the occupational study by Thun et al.

The decline in cadmium levels over time was reflected in the exposure assessment carried out by Thun et al. The effect of arsenic was evaluated by Thun et al., and is discussed in the revised Section VII.J.2 Human studies, Respiratory cancer: Thun study. The hygiene practices of the cohort are not an issue since the risk assessment was based on air monitoring data, and the hygiene practices are irrelevant to lung exposures. Issues related to smoking have been reviewed (see revisions in VII.J.2 Human studies, Respiratory cancer: Thun study).

Comment:

Ciba-Geigy argued that studies of environmental cadmium exposures did not detect adverse health effects.

Response:

The study by Lauwerys (1984) was not concerned with carcinogenicity, but with body burdens of cadmium in relation to nephrotoxicity. With regard to data from Japan, the commentor provided no references.

Comment:

Southern California Edison criticized the ad hoc model which DHS used in its risk assessment, and in particular, the exclusion of data which did not fit the model.

Response:

DHS staff has repeated the risk assessment using a different model which accommodates all the data. (See revised Section IX.B.2)

Comment:

Southern California Edison pointed out that DHS staff incorrectly assumed that the exposures reported by Thun et al. were quantified in units of CdO (cadmium oxide).

Response:

DHS staff acknowledges this error and has corrected it.

Comment:

Southern California Edison questioned the background rate for lung cancer used by DHS on the grounds that it was higher than the rate used by EPA.

Response:

DHS staff has employed 1979-80 California age-specific rates for lung cancer as the background level. The cumulative lifetime probability of

dying of lung cancer by age 80 in California is .055 for males and .025 for females. (See Appendix D in the revised document.)

Comment:

Southern California Edison objected to the use of a nonthreshold model, citing the lack of elevated cancer risk in the lowest exposure group of the study by Thun et al.

Response:

The use of a nonthreshold model is based on theoretical, biological considerations. The staff of DHS does not consider occupational epidemiological studies to be adequate for evaluating whether a threshold process is responsible for inducing cancer. Occupational mortality studies have no ability to distinguish mechanisms by which an effect is induced. The threshold issue is discussed with regard to the mechanisms specific for cadmium-induced carcinogenicity in revised Section VIII. With regard to the data of Thun et al., the lack of response in the low exposure group can be explained as a manifestation of the healthy worker effect, which was also observed for cardiovascular deaths.

Comment:

Southern California Edison argued that the evidence for human carcinogenicity is not sufficient and that the position of DHS was not justified.

Response:

DHS staff has revised the document and has determined that such a judgement was unnecessary because there is sufficient evidence to consider cadmium an animal carcinogen and therefore a potential human carcinogen. (Refer to revised Section VII.J.4 CANCER: Conclusion and to DHS staff responses to SRP comments.)

Comment:

Southern California Edison pointed out that the combined effects of smoking and arsenic may be greater than the sum of the two.

Response:

DHS staff acknowledges that confounding by either of these two risk factors and by their interaction could explain some of the excess lung cancer deaths. Because of the low levels of arsenic and the data indicating a deficit of smokers in the cohort, those two factors are unlikely to account for all of the excess, even assuming a multiplicative effect of arsenic and smoking. (A full discussion is in the revised Section VII.J.2, Human studies, Respiratory cancer-Thun study. Also, see Tables VII-11 to VII-14, especially VII-14.)

Comment:

Southern California Edison argued that the DHS should refrain from recommending upper bound risk estimates until results are available from the nested case/control study being conducted by Thun et al., and until uncertainties in this study have been resolved.

Response:

The DHS is mandated to provide a quantitative risk assessment under California Health and Safety Code 39660. We have attempted to utilize all of the most recent available data in our evaluations and estimates of risk, including the presentations by Dr. Lamm and Dr. Thun at the Fifth International Cadmium Conference. In the revised risk assessment, DHS staff has attempted to clarify areas of uncertainty arising from the data.

Comment:

The Cadmium Council, Inc., argued that the evidence of human carcinogenicity is inadequate and that the critical epidemiological study by Thun et al. is still being reanalyzed. They cited several critisims of this

study: (a) individual estimates of arsenic exposure were not obtained, (b) potential interactive effects of arsenic and smoking were not evaluated. They also submitted several unpublished documents including a manuscript by Dr. George Kazantzis describing a further follow-up of an earlier study of a cohort of workers potentially exposed to cadmium, and a nested case/control study of lung cancer deaths in the cohort.

Response:

The weakness in not having individual arsenic exposure estimates is a concern, but the cohort calculations of Thun et al. indicate that the contribution of arsenic to the excess lung cancer death rate was not large. Evidence presented in the update of this study indicate that arsenic levels have been quite low since 1926, in contrast to the assertions of Dr. Lamm. The issue of interaction is discussed in our revised document. Given the deficit of smokers in the cohort relative to the general population and the low overall risk from arsenic, the interaction of smoking and arsenic exposure is likely to have made a negligible contribution to the excess cancer mortality. This is because at low relative risks, a multiplicative effect is only negligibly different from an additive effect. The case/control study conducted by Kazantzis purports to show no association between cadmium exposure and lung cancer mortality. Although the report contains numerous inconsistencies and is therefore difficult to follow, it appears that the (nonstatistically significant) estimate of relative risk associated with a decade of exposure to 1 $\mu g/m^3$ cadmium was almost identical to the (statistically significant) relative risk associated with a "decade level" of arsenic exposure, with arsenic exposure classified on a scale of 0 to 2. Rather than being strong evidence of no effect, these data show weak evidence of an effect. Furthermore, the exposures of these workers were

much lower than those in the study by Thun et al. Only 21 workers received exposures that were anywhere near as large as the median of the low exposure group in the Thun study. As Kazantzis states, "The present results are not inconsistent therefore with Thun's, but there is very little power to detect a cadmium effect."

Comment:

The Cadmium Council, Inc., objected to the statement by DHS that we "do not believe there is evidence to reject an effect of cadmium on prostatic cancer." They asserted that the statistical evidence is convincing that no effect exists.

Response:

The DHS disagrees that a conclusion of no effect is justified. The reasons were presented in the original document (pp. 66-68 of part B): (1) the highly significant early reports, (2) the persistence of small (nonstatistically significant) elevated risks in recent studies, (3) the decline in level of industrial exposure, and (4) the low statistical power of these studies. In total, DHS staff regards the evidence as inconclusive. For clarification, the sentence referred to by the Cadmium Council, Inc., has been changed to state "the staff of DHS does not believe that the evidence is conclusive to reject an effect of cadmium on prostate cancer."

Comment:

The Cadmium Council, Inc., stated that although EPA's Science Advisory Board (SAB) found the Takenaka study to be sufficient evidence of cadmium's ability to cause cancer in animals, the SAB felt that more information was needed on the actual particle size distribution of ambient cadmium to which the general public would be exposed. This information would allow a comparison for the purpose of quantitative risk assessment, of the effective dose given to the rats in the Takenaka study with typical human exposure.

Response:

The ARB did not estimate the distribution of particle size in ambient California air. However, since the animal study was not used for final risk estimates, it is not really necessary for a comparison of effective dose. If such a comparison were made, it is likely that a modification in ambient exposure could be made that would reflect a lower exposure to cadmium because some ambient particles containing cadmium would not be respirable. In our assessment with occupational exposure, it was assumed that the particle size distribution in the occupational setting and in ambient air were similar. The validity of this assumption cannot be verified.

Comment:

The Cadmium Council, Inc., asserted that the effect of solubility on the bioavailability of various cadmium compounds would be likely to result in a difference in their toxic potency. The ARB draft document indicated that absorption may not be dependent on solubility, citing a study which compared the pharmacokinetics of cadmium chloride and cadmium oxide in the lung. Information on cadmium red and yellow pigments suggests that solubility is important.

Response:

The statement in the ARB document has been changed to explicitly pertain only to cadmium chloride and cadmium oxide. It is important to note that the ARB has concluded that cadmium oxide, cadmium carbonate, and cadmium sulfate are the likely principal constituents of ambient airborne cadmium. Cadmium sulfate is soluble, while the oxide, which is relatively insoluble, appears to act in the lung like cadmium chloride, a soluble salt. It is not known how cadmium carbonate acts in the lung. However, in an unpublished paper by Rusch et al. that was supplied by commentors, cadmium carbonate appeared to be much more soluble and more toxic than cadmium red

or yellow pigments following inhalation. Since there has been no speciation of ambient airborne cadmium DHS staff has assumed that all inhaled cadmium will act as if it were soluble.

Comment:

Ciba-Geigy argued that since cadmium chloride increases both epithelial permeability and the number of inflammatory cells in the lung, the continual presence of this chemical in the lung without any possibility for lung clearance and repair was probably responsible for the increased tumor incidence observed in the study by Takenaka et al.

Response:

Although nontumor pathology was not reported in great detail in the Takenaka study, there is little reason to believe that there had been significant pulmonary lesions as suggested by the commenter. A dose-related increase in lung fibrosis was found in the treated animals of the Takenaka study, but the severity of the lesions and any relationship they have with the observed tumors is unknown (personal communication with Gunter Oberdorster, 2/18/86). Lung damage was likely to have been minimal since all groups of rats experienced a low mortality rate, indicating that the animals were in apparent good health during the study. In addition, a study by Hart (Toxicol Appl Pharmacol 82:281-291, 1985), in which rats were exposed to cadmium oxide at 1.6 mg/m^3, three hours per day, five days per week for six weeks, indicated that the effects mentioned by the commentor would resolve after a few weeks even while exposure continued. The exposure concentration used by Hart was 32 times higher than the highest concentration used by Takenaka, or 4 times greater if averaged over a 24-hour period. Thus, there is not sufficient evidence to suggest that lung defense mechanisms were overwhelmed during the Takenaka study.

Comment:

Ciba-Geigy stated that there are disproportionate changes in tumor incidence with successive dose halving in the Takenaka study. It appears likely that lower dosages caused less lung damage (considered a threshold event) and consequently fewer lung tumors. This would indicate that ambient airborne cadmium does not pose a carcinogenic risk to the general population and should not be classified as a toxic air contaminant.

Response:

As previously stated, the staff of DHS does not consider that there is sufficient evidence to link lung damage with the carcinogenicity of cadmium in rat lungs. Although there was an apparent dose-related increase in fibrosis in the lungs of treated animals (personal communication with Gunter Oberdorster), the severity of the lesions is unknown and a relationship, if any, between these lesions and lung cancer has not been determined. The staff of DHS does not consider a nonlinear dose-response curve in an animal study adequate evidence that a threshold process is responsible for carcinogenicity.

Comment:

Ciba-Geigy pointed out that cadmium compounds are not equivalent with respect to toxicity, absorption, distribution or excretion. Exposure to the two insoluble compounds, cadmium red and cadmium yellow, did not produce mortality and resulted in more rapid elimination, according to an unpublished study by Rusch. Other studies have also shown solubility and physical state of cadmium compounds to be important determinants of potency.

Response:

As stated in response to a similar comment by the Cadmium Council, Inc., the staff of DHS agrees that the toxic and possibly the carcinogenic potency of cadmium compounds could be related to their solubility. It

should be noted that cadmium carbonate and cadmium fume (oxide) were found by Rusch to be more toxic than the cadmium pigments. According to ARB, the carbonate and oxide forms of cadmium are more likely to be found in the ambient air.

Comment:

Ciba-Geigy stated that the doses in the Takenaka study imposed a lung burden on the rats that bears no relationship to effects expected from either larger amounts given for shorter periods or low-level ambient exposures of the general population.

Response:

The staff of DHS does not find the evidence cited by the commentor sufficient to indicate that the lung burden of cadmium imposed on the rats in the Takenaka study was unrepresentative of what might be expected from ambient exposure. Metallothionein levels probably do increase in response to cadmium exposure and it probably does act as a defense mechanism. Hart (1986) showed an increase in lung metallothionein over a six-week period during which the animals were receiving a daily dose four times the highest daily dose given to rats in the Takenaka study. During the six-week period initial lung lesions began to resolve, suggesting that metallothionein may decrease the toxicity of cadmium. There was no evidence that lung metallothionein synthesis was saturated during the Hart study. Thus, there is no reason to believe that rats in the Takenaka study were exposed to a cadmium concentration that would saturate this defense mechanism.

Department of Health Services

Responses to Public Comments on

Health Effects of Cadmium (Revised)

(June 1986 Draft)

Comment:

All 4 commentors (Ciba-Geigy, PG & E, Western Oil & Gas Association, and the California Council for Environmental and Economic Balance) raised the issue of thresholds in the cadmium risk assessment, and urged DHS to present a threshold model to provide a lower bound of risk. The EPA risk assessment of cadmium was cited for its presentation of both threshold and nonthreshold models.

Response:

The position of the Department of Health Services (DHS) with regard to the use of nonthreshold models is presented in the Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale (DHS, 1985):

> "...the DHS guidelines for risk assessment will not include the concept of 'thresholds' for carcinogenesis unless clear and convincing evidence is presented to demonstrate their existence for a specific carcinogen in specified circumstances"

The full discussion of thresholds from that document is attached and is incorporated by reference (Attachment A). The staff of DHS reiterates the arguments related to the mechanisms of cadmium-induced carcinogenicity in the responses to specific comments below:

Comment:

Ciba-Geigy contended that,

> "...the absence of a carcinogenic effect in the Thun study at the two lowest doses indicates that a threshold does exist even in the workplace and would exist for ambient air where exposure is a thousandfold less."

Response:

Lack of an elevated risk among workers in occupational cohorts exposed at low doses does not necessarily constitute evidence of a threshold, but rather evidence of the well-established "healthy worker effect". As explained in the document, these workers were estimated to have half the cancer risk of the U.S. population. Deaths from diseases of the circulatory system were also significantly lower than expected for the whole cohort (SMR=65), providing further evidence of a pronounced healthy worker effect in this cohort. In addition, the size of the study population was too small to detect the magnitude of risks expected at the low doses. Unless one compares the mortality to another worker population, the "expected" lung cancer deaths (obtained from the standard population, in this case 3.77) will be higher than what is predicted by the model at low doses (2.49 lung cancer deaths). This is because the number of expected cases is based on a population which differs from the study population on factors other than exposure to occupational carcinogens; correcting the "expected" for these differences yielded an adjusted value of 1.89 expected lung cancer deaths. Thus, taking into account the estimated healthy worker effect, this study had a power of less than 1% to reject a hypothesis of no-effect for the low dose group at the α=0.05 level, assuming the model predictions are correct. In other words, one would not have expected to detect an excess in lung cancer deaths in the low-dose group.

With regard to the EPA's risk assessment, neither of the models fitted by the EPA (the threshold or the nonthreshold model) fits the observed data as well as the model used by the DHS staff (Table C-1). The poorest fit was obtained by the threshold model for the low-dose group, where the model

fitted by the DHS staff was superior to both models presented by EPA. While all of these models were subject to the limitations of the data, the model that includes a parameter for the healthy worker effect is clearly a better specification of the quantitative dose-response relationship.

Comment:

In their comment on the threshold issue Ciba-Geigy stated:

> "It is of interest that your reviewers consider negative *in vivo* mutation studies as being insensitive tests as opposed to being indicative that the body can effectively handle small doses of cadmium; i.e., exhibit threshold characteristics, at concentrations that might be present in ambient air."

Response:

One interpretation of the results from these studies is that the body can effectively handle small doses of Cadmium. However, DHS staff members have concluded that in this case the interpretation is not valid because this type of assay is relatively insensitive; i.e., this assay is incapable of detecting other than large effects. The dominant lethal assay has a lower sensitivity than other genotoxicity assays because there is: (1) a relatively high rate of spontaneous lethal events that occur during development, and (2) the number of implants examined is extremely small compared to studies that examined individual cells for an effect. In addition, the DHS staff members agree with the International Agency for Research on Cancer (IARC, 1983) that it is difficult to rule out genotoxic effects based on short-term tests and there is insufficient evidence to justify creating a separate class of carcinogens (based on mechanism) for which different risk assessment methods would be used.

Comment:

Ciba-Geigy argued for the concept of a threshold for cadmium-induced carcinogenicity with the following:

> "First of all, excess cadmium can stimulate metallothionein synthesis which is known to detoxify cadmium following continuous low level exposure (Webb, M. (1979) in "Metallothionein", Kagi & Nordberg, editors, pp 313-20). Secondly, it is known that zinc and cadmium interact and compete for protein and enzyme binding sites."

Response:

As stated by the commentor, cadmium does induce metallothionein synthesis and this protein appears to have a protective role against cadmium toxicity. Hart (1986) showed that metallothionein increased during a six-week exposure period when rats were exposed to a cadmium oxide concentration of 1.6 mg Cd/m^3. Metallothionein, however, does not protect against acute cadmium toxicity (Webb 1979). Furthermore, Takenaka et al. (1983) showed that cadmium induced lung cancer at lower exposure levels than were used by Hart. Thus, metallothionein does not appear to prevent cadmium carcingenicity at exposure levels used in the Takenaka et al. study. Metallothionein may have a protective role, but it clearly cannot detoxify all cadmium that enters the body.

Zinc also appears to protect against cadmium toxicity. However, as with metallothionein, there is no evidence that zinc will protect an animal from the carcinogenic effects of cadmium below some specific exposure level. In addition, it is well established that a carcinogen's potency can be inhibited or enhanced by other compounds. Such effects do not indicate that a threshold therefore exists for carcinogenicity.

Comment:

The California Council for Environmental and Economic Balance (CCEEB) suggested that "the Air Resources Board needs to know the relative weight of the evidence regarding the plausibility of such thresholds."

Response:

In the case of cadmium, there is no compelling evidence that the carcinogenic effects are mediated by a threshold. This point is discussed at length in Part B Section VIII.

Comment:

PG & E contended that:

> "Although the DHS qualifies its estimate of 2-12 cases per million by stating that 'the actual risk may lie in or below that range', this is not sufficient since other experts have acknowledged that a zero risk estimate could be equally valid." (citing EPA, 1985)

Response:

The DHS staff believes that the presentation of the range of risk estimates as an upper bound is clear, and that the possibility of lower risk is sufficiently described in Part B, Section IX.

There is neither a theoretical basis nor empirical data sufficient to assign a probability to either the lower or upper bound region. Thus, it is not possible to give a relative weight to one or another portion within this range of risks. In the interest of protecting the public's health, and for reasons cited in Part B of the document and reiterated below, the DHS staff recommends that risk management decisions be based on the upper limit of this range: 30 excess lifetime cancer deaths per million persons from lifetime exposure to current average ambient levels of 2.5 ng/m^3 cadmium.

Comment:

CCEEB stated:

"We can understand the basis for incorporation of the worst-case policy assumptions DHS uses to emphasize the maximum possible upper bound risk (although we believe that risk assessments should also present the 'most likely' risk estimate)."

Response:

As pointed out in Part B Section IX.2, this risk assessment does not present a worst-case scenario, but rather a plausible risk estimate, for the following reasons: (1) the estimate is based on the observed data and on realistic assumptions where data were lacking, both for exposure and for mortality in the study by Thun et al.; (2) the linear extrapolation model is, in the best scientific judgment of the DHS staff, a health-conservative method of extrapolation, while a worst-case would include a supralinear model; (3) the exposure estimate for California residents is based on mean levels obtained from monitoring throughout the urban areas of the state, not on the maxima; (4) as explained extensively in the document, the DHS staff recommends the human-based risk estimates, rather than the higher, animal-based estimates (Part B, Section IX.B.3). Thus, the estimated unit risk and its upper 0.95 confidence limit recommended by DHS provide a plausible range for the upper bound of risk, not a worst-case range.

Comment:

PG & E argued that the DHS risk assessment should recommend the "best" risk estimate rather than the "upper bound."

Response:

As discussed above, the DHS staff has presented a risk estimate based on plausible assumptions, not a worst-case scenario. The main source of

"health-conservatism" is in the use of a linear nonthreshold extrapolation model. The recommendation to use the upper bound on risk is based on two considerations: (1) as discussed in the document (Section VII.J.2), the risk estimate was based on lung cancer deaths only, whereas the epidemiologic evidence suggests urogenital cancer, as well. The data cannot be considered conclusive due to the small sizes of the study cohorts; nevertheless, the recommended risk estimate should provide an added margin of safety for possible increases in these cancers. (2) The application of a dose-response relationship observed in adult males to the general population assumes equal exposure and sensitivity across all ages and sexes. Since our risk assessment is based on average levels obtained at monitoring stations, this assumption could result in an underestimation of risk for several reasons:

The rapidly proliferating tissues of children may be more susceptible to carcinogenic agents than cells in adults. Second, where air concentrations of cadmium may be related to dust from contaminated soil, children are not only closer to the ground, but far more likely to play in dirt and thus to have substantially higher exposures than adults. Third, a recent paper by Phalen et al. (1985) showed that tracheobronchial particle deposition is generally more efficient in smaller (younger) individuals than in larger (older) people. For instance, the dose on a per kg basis for 5 μm diameter particles could be 6 times higher in a resting newborn than in a resting adult. This paper also showed that particle deposition varies with activity level. It appears, therefore, that at ages when individuals are potentially more susceptible to carcinogenic damage, they may be

consistently receiving higher exposures and distributing cadmium to the target site more efficiently.

For these reasons, the DHS staff does not concur with the conclusion of EPA (1985) that the upper bound risk estimate provides an "unnecessary added level of conservatism."

Comment:

Ciba-Geigy noted that the DHS staff did not take into account the potential effect of dose-rate on cadmium's carcinogenic activity, citing several studies.

Response:

The observations of Littlefield and Gaylor (1985), cited by the commentors, were based on the ED_{01} study of 2-acetylaminofluorene. Since the dose-rate characteristics of a compound's carcinogenicity may be dependent on the pathways for metabolic handling by the organism, this study does not necessarily apply to cadmium. The contrast between survival rates in the studies by Oldiges and Glaser (1986) and by Kaplan et al. (1977), also cited by the commentors, reflects a dose-rate effect of cadmium on noncarcinogenic toxicity, which may not generalize to carcinogenicity. Additionally, it is difficult to draw a conclusion based on a comparison of these two studies since they were done in different laboratories and with different strains of rats. DHS staff members, however, do recognize that dose-rate may influence the carcinogenic risks due to cadmium exposure. Because this effect has not been characterized quantitatively, the assumption was made that, in the absence of data, cumulative dose could define risk (Part B, Section IX.B.2). This is a health-protective assumption, since the environmental exposures involve much lower dose-rates,

as well as lower cumulative doses, than were used to estimate the carcinogenic potency of cadmium.

Comment:

Western Oil and Gas Association (WOGA) suggested that converting doses between species by direct air concentrations, i.e., not accounting for differences in metabolic rate, constituted manipulation of the data.

Response:

DHS staff conducted its animal-based risk assessment by converting rat to human doses on a surface-area basis. In the discussion comparing the animal- and human-based risk assessments, a risk estimate was derived in which direct air concentration in the animal experiment was taken to be equivalent to the human dose. As explained in Part B, Section IX.B.3, this calculation was presented for comparative purposes only, and does not, in the staff's opinion, constitute manipulation of the data.

Comment:

WOGA stated that the DHS staff's use of human data for the cadmium risk assessment is inconsistent with the previous use of animal data when human data were available for benzene.

Response:

The range of risk estimates (24×10^{-6} to 170×10^{-6}) recommended by DHS staff for the benzene risk assessment (DHS, 1984) was based on both the EPA estimate, which used data from three epidemiologic studies of leukemia deaths, and an estimate derived from a National Toxicology Program cancer bioassay in male mice. A comparison of the risk estimates and confidence intervals from the linear extrapolation using the best quality human data (Rinsky et al. 1981) and the multistage model using the most sensitive

animal data (preputial gland tumors in mice) shows both the point estimates and the upper 95% confidence limits (CL) to be very close:

RISK DUE TO 1 PPB AMBIENT EXPOSURE TO BENZENE

	Epidemiologic Data	Animal Data
Point Estimate	48×10^{-6}	78×10^{-6}
Upper 95% CL	120×10^{-6}	170×10^{-6}

Unlike benzene, for cadmium, the confidence intervals for the animal- and human-based risk estimates did not overlap. Therefore, the DHS staff felt that it was necessary to make a choice. For reasons stated at length in the document (Section IX.B.3), the choice to recommend risk estimates based on human data was dictated by both the quality of the epidemiologic data, (including the exposure information and the analysis of potential confounders) and our judgment that the assumptions were unlikely to result in an underestimate of the true risk. The approach taken by DHS staff for the cadmium risk analysis was therefore fully consistent with methods utilized in previous risk analyses.

Comment:

Ciba-Geigy stated that possible exposures to asbestos and to radon were not considered in the study by Thun et al. (1985) and that these could have been confounders. The commentor asserted that one of the lung cancer deaths was a worker who was also in another cohort where his death was attributed to asbestos.

Response:

It is possible that one of the workers in the study of Thun et al. may have left this plant and then worked elsewhere and received asbestos

exposure. Whether or not this is true, workers in the comparison population have similar opportunities to receive asbestos exposures. Since it is a relatively common exposure, asbestos-induced lung cancers contribute to the background rates throughout the U.S. Furthermore, if it is true that asbestos exposure contributed to the death of one of the cadmium-exposed workers, one cannot rule out an added contribution from cadmium, given the multifactorial nature of carcinogenesis. It is also unlikely that exclusion of this death would substantially alter the result of the risk assessment (e.g., compare the upper and lower portions of Table IX in Part B of the document). Dr. Thun, in a personal communication (9-9-86) indicated that in a further follow-up of the cohort to 1984, the lung cancer deaths continued to show a dose-response relationship to cadmium exposure.

The probability of significant radon exposures in the plant is low. The plant itself is above ground, so that if radon gas were emitted by soil, it would readily diffuse; containment such as occurs in mines or basements would not occur. If radon exposures were a problem in that region, one would expect a less pronounced effect when comparing to state rates as opposed to U.S. rates. The SMRs were higher, not lower, when the state rates were used as a comparison. Further, if radon daughters were being emitted from mill tailings in the walls, it would be highly coincidental if those portions of the plant where cadmium exposures were greater also had higher radon exposures.

While it is difficult to entirely rule out the potential for confounding from unmeasured sources such as radon and asbestos, the plausibility of these sources as explanations for the clear dose-response

between well-quantified cadmium exposures and excess mortality from lung cancer is low.

Comment:

Ciba-Geigy pointed out that the use of an occupational standard for cadmium to produce a safe ambient level yields a value which is three times as great as levels measured in "hot spots" in California, and fifty times as great as average ambient levels. The commentor cited Calabrese (1986) as saying that this method is "consistently more conservative or protective than that derived from actual data."

Response:

This method involves dividing the TLV (threshold limit value) by the ratio of hours in a workweek to total hours in a week, and then applying a safety factor of 100. The above quotation referred to 5 pollutants regulated by the U.S. federal government. In the same paper, Calabrese reported that this method applied to maximum acceptable occupational levels in the Soviet Union is more protective than the direct use of experimental data for 30 pollutants, and less protective for 13 others. Based on the figures provided by Ciba-Geigy for cadmium, this method is clearly less protective than the estimates EPA or DHS staff derived using the actual data. In the U.S., TLVs do not represent a uniform concept: they are principally based on considerations other than carcinogenicity, and may be based on practical considerations of what is attainable. In the case of cadmium, the ACGIH based its recommended TLV on kidney toxicity (ACGIH, 1982).

Comment:

Ciba-Geigy referred to evidence that cigarette smoking contributes to the body burden of cadmium, citing a study which showed that smokers' lungs contained a protein which binds cadmium.

Response:

DHS staff acknowledges that cigarette smoking can increase the cadmium body burden. It may contribute to the production of cadmium-binding proteins. However, this does not constitute evidence of the safety of ambient levels of cadmium. It is also possible that cadmium is one of the components of cigarette smoke which is responsible for its strongly carcinogenic effect.

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TABLE C-1

A COMPARISON OF THE OBSERVED DATA OF THUN ET AL.
AND THE PREDICTED RISKS FROM THREE MODELS

	Low	Middle	High	$\chi^2_{(df)}$*	p-value
OBSERVED:	2	7	7		
PREDICTED:					
EPA Nonthreshold Model	4.53	7.33	6.08	$1.6_{(2)}$	.45
EPA Threshold Model	3.77	4.61	7.00	$2.1_{(1)}$	.15
DHS Nonthreshold Model with Healthy Worker Effect	2.94	5.99	7.44	$0.5_{(1)}$	.48

* df=degrees of freedom

Issues in the Selection of Dose-Response Models

1. Thresholds

Traditional toxicology incorporates thresholds in the dose-response relationship. These are dose levels below which a toxicological response is not observed. This is not to imply that cellular or tissue damage does not occur below the "threshold" level, but rather that the organism either has the reserve capacity to withstand damage or is able to adapt to the toxicological stress. For toxicologic effects, a threshold is said to occur at dose levels that are insufficient to cause damage. For example, if a toxic substance killed nonreplicating optical neurons, sight would not suffer until a sufficiently large number (perhaps millions) of cells had died.

But the processes of carcinogenesis appear to be qualitatively different from those in classical toxicology. In contrast to the toxic effects described above which involve impairment of functions at the organ or organism level, the initial "target" for carcinogenic action is believed to be extremely small. As we develop a better understanding of the mechanisms of carcinogenesis and mutagenesis, it appears likely that many carcinogens interact with DNA or other target macromolecules. In addition, there is evidence that the occurrence of such events in a single cell can produce cancer.[28,29] The delivery of the critical molecules to critical cell at the critical time involves the interplay of a variety of protective defense systems within the body. However, there is some finite probability that a few molecules would evade these defenses and produce an event that triggers carcinogenesis. This scenario, so different from classic toxicologic processes, makes a threshold less likely for carcinogenesis.

Despite this, a pharmacokinetic argument has been made for the existence of practical operation thresholds. For example, the observation of a plateau of response at the high dose levels of the vinyl chloride dose-response curve is interpreted to mean that the enzyme system(s) that <u>activate</u> vinyl chloride to its carcinogenic species are overloaded or saturated. The argument is then made by analogy that protective enzymes systems that <u>deactivate</u> carcinogens and are reasonably effective at low doses may likewise be saturated and hence be less protective at the high doses encountered in animal bioassays.[30-34]

A model that produces a threshold in the dose-response curve has been developed. This model is based on the concept that high doses of carcinogens can overcome protective systems. However, this model produces a threshold by requiring that the carcinogen be instantaneously deactivated, which is unlikely. If detoxification reactions are not instantaneous, a small amount of the agent may escape detoxification by protective enzymes and interact with the DNA. In this instance, the protective effect of detoxifying enzymes would decrease the slope of the dose-response curve but would not produce a classical threshold.[35]

Even if thresholds could be determined for individuals, establishing a population threshold is more difficult because of the observed variability of the human population. This variation is a consequence of extreme genetic heterogeneity and differences in physiological state associated with age, sex, reproductive activities, nutrition, and exposure to environmental/ occupational stresses including other carcinogens. Even if it is assumed that each individual in the population has a threshold defined (at any one time) by his or her physiological state, the population is likely to be characterized by a very wide distribution of thresholds such that there may not be an absolute lower bound or population threshold.[6,36,37] Since the threshold dose for the human population should be the threshold dose for the most sensitive individual, this dose may be so low as to be effectively zero. By analogy, the threshold dose for an individual or organism is the threshold dose for the most sensitive cell, and this may also be extremely low.[38] Operationally, these variable threshold models are difficult to distinguish from nonthreshold models that are concave upward at low doses.

These models would produce absolute thresholds only under the assumptions of instantaneous deactivation and repair. Other models[39] predict nonlinearities in the dose-response curve that will lead to practical, but not absolute, thresholds. The presence, or absence, of an absolute threshold remains unconfirmable. The EDO1 study indicated that the 2-AAF mouse exhibits an apparent threshold for bladder cancers at low doses. However, re-analysis of this low-dose data at greater resolution indicated that the threshold was more apparent than real: the incidence of bladder tumors increased with dose even at the low doses, and no threshold level could be determined.[9] Thus, scientists are now less concerned with the existence of thresholds than in the degree of nonlinearity of the dose-response curve in the low dose region.

Another factor against the existence of thresholds for carcinogens is the substantial "background" incidence of cancer in humans. Unless each carcinogenic substance operates by a unique mechanism, an additional small exposure to a substance may supplement an individual's exposure to other carcinogens operating by a similar mechanism. The high incidence of cancer of unexplained etiology demonstrates that human exposure is well in excess of any possible population threshold for at least some of these mechanisms. Viewed in this manner, since we cannot know which of the possible carcinogenic mechanisms are already operating and contributing to background incidence, we will assume that no additional exposure, however small, may be considered free of risk.

For these reasons, the DHS guidelines for risk assessment will not include the concept of "thresholds" for carcinogenesis unless clear and convincing evidence is presented to demonstrate their existence for a specific carcinogen in specified circumstances (NAS[6,7], OSHA[8], OTA[9], Food Safety Council[10,11]).

Memorandum

To : William Lockett, Chief
Office of External Affairs
Air Resources Board
1102 Q Street
Sacramento, CA 95812

Date : October 10, 1986

Subject: Response to Ciba-Geigy letter on Cadmium

From : Epidemiological Studies
and Surveillance Section
714 P Street
Sacramento, CA 95814

I have reviewed the comments and information contained in a letter addressed to Mr. Cliff Popejoy of the California Air Resources Board from Dr. Martin E. Bernstein of Ciba-Geigy Corporation dated June 18, 1986. I found the comments similar to those submitted earlier by Ciba-Geigy and the Cadmium Council. These comments point out that there is a difference in the toxic potency of various cadmium compounds probably due to the difference in solubility. In particular, cadmium sulfide is less toxic than cadmium oxide or cadmium chloride.

It is evident from the information submitted in this letter and in the earlier submissions that there is a difference in toxicity. In a previous set of responses (letter from Gary Murchison of ARB containing an addendum to the Draft Report on Cadmium, dated July 17, 1986), staff of the Department of Health Services indicated that such a difference does exist (pages 7 and 9).

I would like to point out that cadmium oxide, sulfate, and carbonate are considered the primary species of cadmium in ambient California air. Evidence indicates that these compounds act more like cadmium chloride, which was shown to be carcinogenic in an animal bioassay, than cadmium sulfide, which the commentor has indicated is less toxic than other cadmium compounds.

In the final paragraph of the letter, it was stated that no neoplastic lesions had been found in exposed animals that were part of the on going study cited in the letter. I believe it is premature to determine the adequacy of this study since the study is still in progress and the only pathology results appear to be for animals exposed for less than one year.

If you have any questions, please call me at 324-2829.

David M. Siegel, Ph.D.
Staff Toxicologist

cc: Michael Lipsett
Raymond Neutra

INTRODUCTION AND RECOMMENDATION

State law defines a toxic air contaminant as an air pollutant which the Air Resources Board or the Department of Food and Agriculture finds "may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health". The staffs of the Air Resources Board and Department of Health Services have reviewed the available scientific evidence on the presence of cadmium in the atmosphere of California and its potential adverse effect on public health. Based on the conclusion of the Department of Health Services staff that cadmium meets this definition, the staff of the Air Resources Board recommends that cadmium be identified by the Board as a toxic air contaminant. The ARB staff is unable to, based on available scientific information, identify a level below which adverse health effects are not expected to occur, and therefore is unable to recommend a threshold level.

Cadmium was chosen for evaluation because: it had been identified by the International Agency for Research on Cancer (IARC) as an animal carcinogen with epidemiological evidence of carcinogenicity in humans; its presence in the atmosphere had been documented; it is emitted from many sources in the state, and may be emitted in increased amounts in the future.

SOURCES OF CADMIUM

Cadmium is emitted from both stationary and mobile sources. Stationary sources which are likely to emit cadmium include secondary smelters, cement

manufacturing plants, cadmium electroplating facilities, plants burning oil or coal, and sewage sludge incinerators. Mobile sources which emit cadmium include gasoline and diesel vehicles and particles resulting from tire wear. An emissions inventory compiled by ARB staff indicates that a total of from 16 to 18 tons/year of cadmium are emitted in California; stationary sources account for eighty percent or more of cadmium emissions. Cadmium emissions from fossil fuel combustion and vehicles are projected to increase due to expected increase in fuel use.

EXPOSURE TO ATMOSPHERIC CADMIUM

General population exposure to atmospheric cadmium was estimated using data on cadmium concentrations for the first six months of 1985 in various locations in the state. We believe that these averages are reasonably representative of annual average concentrations. We estimate that 10 million people are exposed to an average cadmium concentration of 1.0 to 2.5 ng/m^3, and that one million people are exposed to an average cadmium concentration of 1.8 to 5.6 ng/m^3. Neither size distribution nor the compound forms of cadmium were determined in the ARB's measurements. Work done by others on the size distribution of atmospheric cadmium indicates that atmospheric cadmium occurs principally on the surface of respirable particles (those less than 2.5 micrometers (um) in diameter).

Exposure to atmospheric cadmium near sources is expected to be higher than general population exposure. To estimate exposure to atmospheric cadmium near sources, ARB staff used on air quality model to calculate the ambient concentration of atmospheric cadmium in the South Coast Air Basin due to emissions from three secondary copper smelters. These emissions were

estimated to result in annual average exposure to atmospheric cadmium of up to 40 ng/m^3 for a population of 57,000 and 14 up to ng/m^3 for a population of 285,000.

HEALTH EFFECTS OF CADMIUM

Concentrations of cadmium measured in the atmosphere are much lower than those which are associated with chronic adverse health effects in occupational settings or which have produced acute effects in animal experiments. Because of this, and because cadmium is thought to exhibit a threshold effect for non-cancer health effects, adverse health effects other than cancer are not expected to occur due to inhalation of cadmium at current or anticipated atmospheric concentrations.

Two separate cancer risk assessments were developed, both of which assumed that cadmium carcinogenicity operates through a nonthreshold mechanism. One was based on a mortality study of workers in a cadmium production plant; for exposure to 1 ng/m^3 cadmium, a best estimate of excess lifetime cancer risk of 2 per million, and an upper 95% confidence limit (UCL) of 12 per million, were derived. The other cancer risk assessment was based on rat lung tumor incidence; risk estimates derived from these studies were higher than the human-based estimates. The DHS staff has determined that the possible roles of chance, bias and confounding factors in distorting the true dose-response relationship in the occupational study were likely to have been small. Because the human data for exposure and for response were not found to have any major deficiencies, and because a conservative linear extrapolation was used, DHS staff recommends reliance on the human-based risk assessment.

RISK DUE TO ATMOSPHERIC CADMIUM

The hazard posed by atmospheric cadmium to residents of California was estimated by applying the unit risk estimate to cadmium concentrations measured in the state. The upper-bound excess lifetime cancer risk from estimated atmospheric concentrations of cadmium in California has been estimated to be 30 per million. For people near emission sources of cadmium, the upper-bound estimated excess lifetime cancer risk from 24-hour-per-day exposure to an average of 40 ng/m^3 of cadmium is 480 per million persons exposed. These are health-conservative estimates; the actual risks may lie below these values.

Exposures to cadmium via routes other than inhalation of ambient air were not considered in the risk assessment. The major nonoccupational exposures to cadmium are through food and smoking. While the bulk of human intake is via food ingestion, this route of exposure has not been associated with an increased risk of cancer either in humans or in experimental animals.

DHS staff emphasizes that the risk estimates derived in conducting a risk assessment are not exact predictions, but rather represent best estimates based on current scientific knowledge and methods.

Based on the findings of cadmium-induced carcinogenicity and the results of the risk assessment, DHS staff finds that ambient cadmium is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

SUMMARY OF ENVIRONMENTAL IMPACTS OF THE IDENTIFICATION OF CADMIUM AS A TOXIC AIR CONTAMINANT

The identification of cadmium as a toxic air contaminant is not in itself expected to result in any environmental effects. The identification of

cadmium as a toxic air contaminant by the Board may result in the Board and air pollution control districts adopting toxic control measures in accordance with the provisions of state law. Any such toxic control measures may result in reduced emissions of cadmium to the atmosphere, resulting in reduced ambient concentrations, concurrently reducing the health risk due to cadmium. Therefore, the identification of cadmium as a toxic air contaminant may ultimately result in environmental benefits. Environmental impacts identified with respect to specific control measures will be included in the consideration of such control measures pursuant to Health and Safety Code Sections 39665 and 39666.

Amend Title 17, California Administrative Code, Section 93000 to read as follows:

93000. Substances Identified As Toxic Air Contaminants. Each substance identified in this section has been determined by the state board to be a toxic air contaminant as defined in Health and Safety Code Section 39655. If the state board has found there to be a threshold exposure level below which no significant adverse health effects are anticipated from exposure to the identified substance, that level is specified as the threshold determination. If the board has found there to be no threshold exposure level below which no significant adverse health effects are anticipated from exposure to the identified substance, determination of "no threshold" is specified. If the board has found that there is not sufficient available scientific evidence to support the identification of a threshold exposure level, the "Threshold" column specifies "None identified."

Substance	Threshold
Benzene (C_6H_6)	None identified
Ethylene Dibromide ($BrCH_2CH_2Br$; 1,2-dibromoethane)	None identified
Ethylene Dichloride ($ClCH_2CH_2Cl$; 1,2-dichloroethane)	None identified
Hexavalent Chromium, Cr(VI)	None identified
Asbestos [asbestiform varieties of serpentine (chrysotile) riebeckite (crocidolite) cummingtonite-grunerite (amosite), tremolite, actinolite, and anthophyllite]*	None identified
Dibenzo-p-dioxins and Dibenzofurans chlorinated in the 2,3,7 and 8 positions and containing 4,5,6 or 7 chlorine atoms*	None identified
Cadmium	None identified

NOTE: Authority cited: Sections 39600, 39601 and 39662, Health and Safety Code. Reference: Sections 39650, 39660, 39661 and 39662, Health and Safety Code.

*Note: Compounds identified by an asterisk have been identified as toxic air contaminants by the Air Resources Board but not yet approved by the Office of Administrative Law.

Notice of Public Availability of Modified Text

Public Hearing to Consider the Adoption of a Regulatory Amendment Identifying Metallic Cadmium and Cadmium Compounds as Toxic Air Contaminants

Public Hearing Date: January 23, 1987
Public Availability Date: February 9, 1987

At a January 23, 1987 public hearing, the Air Resources Board ("ARB" or the "Board") considered the adoption of a proposed regulatory amendment to list cadmium as a toxic air contaminant for which there is not sufficient available scientific evidence to support the identification of a threshold exposure level. At the hearing the Board approved the proposed amendment with modifications to the originally proposed text. The modification to the originally proposed text is described below. Attached is a copy of Board Resolution 87-9 approving the proposed amendments with modifications. Attached to the resolution is the approved language, with additions to the original proposal shown by double underlining. The unchanged portion of the original proposal is shown by a single underline.

The originally proposed text listed "cadmium" as a toxic air contaminant. Airborne cadmium is generally understood to mean both airborne metallic cadmium and airborne cadmium compounds. Further, the analysis in the staff report to the Air Resources Board applies to both metallic cadmium and cadmium compounds. Staff believes that the term cadmium refers to both forms of cadmium, but decided that the listing of cadmium in the regulation should be made explicit in order to avoid any confusion as to the scope of the Board's action. The Board approved the staff's modified recommendation to include "metallic cadmium and cadmium compounds" in parentheses after "cadmium."

In accordance with Section 11346.8 of the Government Code, the Board directed the Executive Officer to adopt the approved regulatory amendments after making them available to the public for comment regarding the changes to the regulation as originally proposed for a period of at least 15 days provided that the Executive Officer shall consider written comments received and make minor modifications to the language as appropriate in response to comments, and shall present the regulations to the Board for further consideration if he determines that this is warranted in light of the written comments received. Only comments concerning the modified definition of cadmium will be considered during this comment period.

Comments must be submitted to the Board Secretary, Air Resources Board, P. O. Box 2815, Sacramento, CA 95812, no later than March 2, 1987 for consideration by the Executive Officer.

State of California
AIR RESOURCES BOARD

Resolution 87-9

January 23, 1987

Agenda Item No.: 87-2-1

WHEREAS, Sections 39600 and 39601 of the Health and Safety Code authorize the Air Resources Board (the "Board") to do such acts and to adopt such regulations as may be necessary for the proper execution of the powers and duties granted to, and imposed upon, the Board by law;

WHEREAS, Chapter 3.5 (commencing with Section 39650) of Part 2 of Division 26 of the Health and Safety Code establishes procedures for the identification of toxic air contaminants by the Board;

WHEREAS, Section 39655 of the Health and Safety Code defines a "toxic air contaminant" as an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health;

WHEREAS, Section 39662 of the Health and Safety Code directs the Board to list, by regulation, substances determined to be toxic air contaminants, and to specify for each substance listed a threshold exposure level, if any, below which no significant adverse health effects are anticipated;

WHEREAS, in California, cadmium (metallic cadmium and cadmium compounds, hereinafter "cadmium") is emitted from certain industrial processes such as secondary smelting operations, cement manufacturing, and combustion of fossil fuels, and has been measured in the atmosphere;

WHEREAS, pursuant to the request of the Board, the Department of Health Services (DHS) evaluated the health effects of cadmium in accordance with Section 39660 of the Health and Safety Code;

WHEREAS, DHS concluded in its evaluation that cadmium is an animal carcinogen with epidemiological evidence of carcinogenicity in humans; cadmium should be treated as a substance without a carcinogenic threshold; health effects other than cancer are not expected to occur at existing or expected ambient levels of cadmium; and the maximum excess lifetime cancer risk from cadmium exposure is estimated to range from 2 to 12 cases per million people exposed per nanogram per cubic meter;

WHEREAS, for the reasons set forth in its evaluation, DHS has concluded that, in the absence of strong positive evidence that cadmium acts only through mechanisms which ought to have a threshold, cadmium should be treated as acting without a threshold, and DHS has determined that there is not sufficient available scientific evidence at this time to support the identification of a cadmium exposure level below which carcinogenic effects would not have some probability of occurring;

WHEREAS, upon receipt of the DHS evaluation, staff of the Board prepared a report including and in consideration of the DHS evaluation and recommendations and in the form required by Section 39661 of the Health and Safety Code and, in accordance with the provisions of that section, made the report available to the public and submitted it for review to the Scientific Review Panel (SRP) established pursuant to Section 39670 of the Health and Safety Code;

WHEREAS, in accordance with Section 39661 of the Health and Safety Code, the SRP reviewed the staff report, including the scientific procedures and methods used to support the data in the report, the data itself, and the conclusions and assessments on which the report was based, considered the public comments received regarding the report, and on October 30, 1986, adopted for submittal to the Board findings which included the following:

"1. Cadmium is an animal carcinogen for which there is epidemiologic evidence of carcinogenicity in humans exposed in occupational settings.

"2. Cadmium is emitted into the air by a variety of sources in California, and its presence has been documented in the ambient air around the state.

The SRP notes that the sub-population of Californians who smoke tobacco or breathe second-hand tobacco smoke will be exposed to cadmium at concentrations several orders of magnitude greater than the exposure of the general population.

The SRP also wishes to emphasize that estimates of cumulative exposure to cadmium should account for cadmium levels in indoor air which, in the absence of tobacco smoke, may be lower than those in outdoor air.

"3. Adverse health effects other than cancer are not expected to occur at measured or predicted cadmium concentrations in the ambient air.

"4. Based on available scientific information, a cadmium exposure level below which carcinogenic effects are not expected to occur cannot be identified.

"5. Based on an interpretation of available scientific evidence by DHS, the range of lifetime excess cancer risk from exposure to 1 ng/m3 of atmospheric cadmium based on the best estimate of risk and the upper 95% confidence limit is estimated to be 2 to 12 cases per million people exposed; it is unlikely that the risk will exceed this range, and may be lower.

"NOTE: DHS has assumed that the carcinogenic dose response of cadmium is linear and that dose rate does not influence the magnitude of carcinogenic effects. These assumptions are justified by DHS on the basis of being health conservative. While the SRP understands the reasons for this, weighing of the available scientific evidence indicates that the upper bound of the low dose risk estimate obtained by using these assumptions is likely to be high. The available data are also consistent with the possibility that the risk of lung cancer from current ambient exposures to cadmium in Califonia may be vanishingly small."

WHEREAS, the SRP found the staff report to be without serious deficiency, and included in its findings the statement that it agreed that cadmium should be listed by the Air Resources Board as a toxic air contaminant, and that there is not sufficient available scientific evidence at this time to support the designation of an exposure level below which carcinogenic effects would not have some probablility of occurring;

WHEREAS, the California Environmental Quality Act and Board regulations require that no project having significant adverse environmental impacts be adopted as originally proposed if feasible alternatives or mitigation measures are available;

WHEREAS, a public hearing and other administrative proceedings have been held in accordance with provisions of Chapter 3.5 (commencing with Section 11340), Part 1, Division 3, Title 2 of the Government Code;

WHEREAS, in consideration of the staff report, including DHS' evaluation and recommendations, the available evidence, the findings of the SRP, and the written comments and public testimony it has received, the Board finds that:

Cadmium is an animal carcinogen with epidemiological evidence of carcinogenicity in humans;

Health effects other than cancer are not anticipated at existing ambient cadmium exposure levels;

There is not sufficient available scientific evidence to support the identification of a threshold exposure level for cadmium; and

Cadmium is an air pollutant which, because of its carcinogenicity, may cause or contribute to an increase in mortality and an increase in serious illness, and poses a hazard to human health; and

WHEREAS, the Board has determined, pursuant to the requirements of the California Environmental Quality Act and Board regulations, that this regulatory action will have no significant adverse impact on the environment.

NOW, THEREFORE BE IT RESOLVED, that the Board approves the proposed regulatory amendments to Section 93000, Title 17, California Administrative Code, as set forth in Attachment A.

BE IT FURTHER RESOLVED that the Board directs the Executive Officer to adopt the amendments, as set forth in Attachment A, after making it available to the public for a period of 15 days, provided that the Executive Officer shall consider such written comments regarding the changes in the regulations as originally proposed as may be submitted during this period, shall make such modifications as may be appropriate in light of the comments received, and shall present the regulations to the Board for further consideration if he determines that this is warranted.

I hereby certify that the above is a true and correct copy of Resolution 87-9, as adopted by the Air Resources Board.

Harold Holmes, Board Secretary

Amend Title 17, California Administrative Code, Section 93000 to read as follows:

93000. Substances Identified As Toxic Air Contaminants. Each substance identified in this section has been determined by the state board to be a toxic air contaminant as defined in Health and Safety Code Section 39655. If the state board has found there to be a threshold exposure level below which no significant adverse health effects are anticipated from exposure to the identified substance, that level is specified as the threshold determination. If the board has found there to be no threshold exposure level below which no significant adverse health effects are anticipated from exposure to the identified substance, determination of "no threshold" is specified. If the board has found that there is not sufficient available scientific evidence to support the identification of a threshold exposure level, the "Threshold" column specifies "None identified."

Substance	Threshold
Benzene (C_6H_6)	None identified
Ethylene Dibromide ($BrCH_2CH_2Br$; 1,2-dibromoethane)	None identified
Ethylene Dichloride ($ClCH_2CH_2Cl$; 1,2-dichloroethane)	None identified
Hexavalent Chromium, Cr(VI)	None identified
Asbestos [asbestiform varieties of serpentine (chrysotile) riebeckite (crocidolite) cummingtonite-grunerite (amosite), tremolite, actinolite, and anthophyllite]	None identified
Dibenzo-p-dioxins and Dibenzofurans chlorinated in the 2,3,7 and 8 positions and containing 4,5,6 or 7 chlorine atoms*	None identified
Cadmium (metallic cadmium and cadmium compounds)	None identified

NOTE: Authority cited: Sections 39600, 39601 and 39662, Health and Safety Code. Reference: Sections 39650, 39660, 39661 and 39662, Health and Safety Code.

*Note: Compounds identified by an asterisk have been identified as toxic air contaminants by the Air Resources Board but not yet approved by the Office of Administrative Law.

SCIENTIFIC REVIEW PANEL FINDINGS ON THE REPORT TO THE AIR RESOURCES BOARD ON CADMIUM

Findings of the Scientific Review Panel on the Report on Cadmium as adopted at the Panel's October 30, 1986 meeting

In accordance with the provisions of Health and Safety Code Section 39661, the Scientific Review Panel (SRP) has reviewed the reports of the staffs of the ARB and DHS on the public exposure and biologic and health effects of cadmium, and the public comments on these reports. Based on this review, the SRP finds that the reports are without serious deficiency and further finds that:

1. Cadmium is an animal carcinogen for which there is epidemiologic evidence of carcinogenicity in humans exposed in occupational settings.

2. Cadmium is emitted into the air by a variety of sources in California, and its presence has been documented in the ambient air around the state.

   The SRP notes that the sub-population of Californians who smoke tobacco or breathe second-hand tobacco smoke will be exposed to cadmium at concentrations several orders of magnitude greater than the exposure of the general population.

   The SRP also wishes to emphasize that estimates of cumulative exposure to cadmium should account for cadmium levels in indoor air which, in the absence of tobacco smoke, may be lower than those in outdoor air.

3. Adverse health effects other than cancer are not expected to occur at measured or predicted cadmium concentrations in the ambient air.

4. Based on available scientific information, a cadmium exposure level below which carcinogenic effects are not expected to occur cannot be identified.

5. Based on an interpretation of available scientific evidence by DHS, the range of lifetime excess cancer risk from exposure to 1 ng/m3 of atmospheric cadmium based on the best estimate of risk and the upper 95% confidence limit is estimated to be 2 to 12 cases per million people exposed; it is unlikely that the risk will exceed this range, and may be lower.

NOTE: DHS has assumed that the carcinogenic dose response of cadmium is linear and that dose rate does not influence the magnitude of carcinogenic effects. These assumptions are justified by DHS on the basis of being health conservative. While the SRP understands the reasons for this, weighing of the available scientific evidence indicates that the upper bound of the low dose risk estimate obtained by using these assumptions is likely to be high. The available data are also consistent with the possibility that the risk of lung cancer from current ambient exposures to cadmium in California may be vanishingly small.

For these reasons, we agree with the ARB staff recommendation to its Board that cadmium be listed by the ARB as a toxic air contaminant, and we agree there is not sufficient available scientific evidence at this time to support the designation of an exposure level below which carcinogenic effects would not have some probability of occurring.

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on October 30, 1986

Dr. Emil M. Mrak, Chairman
Scientific Review Panel

State of California
AIR RESOURCES BOARD

TECHNICAL SUPPORT DOCUMENT

PUBLIC HEARING TO CONSIDER THE ADOPTION OF A REGULATORY AMENDMENT IDENTIFYING CADMIUM AS A TOXIC AIR CONTAMINANT

Agenda Item No: 87-2-1
Scheduled for Consideration: January 22, 1987
Release Date: December 5, 1986

TABLE OF CONTENTS

I. SUMMARY AND RECOMMENDATION

The staffs of the Air Resources Board and Department of Health Services collected, assessed and integrated the available scientific evidence on the presence of cadmium in the atmosphere of California and its potential adverse effect on public health. This is a summary of the information presented in the resulting report.

State law defines a toxic air contaminant as an air pollutant which the Air Resources Board or the Department of Food and Agriculture finds "may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health". Based on the Department of Health Services staff conclusion that cadmium meets this definition, the staff of the Air Resources Board recommends that cadmium be identified by the Board as a toxic air contaminant. In making this recommendation, the ARB staff is unable to, based on available scientific information, identify a level below which adverse health effects are not anticipated to occur, and is therefore unable to recommend a threshold level.

Cadmium was chosen for evaluation because: it had been identified by the International Agency for Research on Cancer (IARC) as an animal carcinogen with epidemiological evidence of carcinogenicity in humans; its presence in the atmosphere had been documented; it is emitted from many sources in the state, and may be emitted in increased amounts in the future.

Cadmium is emitted from both stationary and mobile sources. Stationary sources which are likely to emit cadmium include secondary smelters, cement manufacturing plants, cadmium electroplating facilities, plants burning oil or

coal, and sewage sludge incinerators. Mobile sources which emit cadmium include gasoline and diesel vehicles and particles resulting from tire wear. An emissions inventory compiled by ARB staff indicates that a total of from 16 to 18 tons/year of cadmium are emitted in California; stationary sources account for eighty percent or more of cadmium emissions. Cadmium emissions from fossil fuel combustion and from vehicles are projected to increase due to expected increases in fuel consumption.

Available evidence suggests that cadmium from certain combustion sources undergoes atmospheric reactions which lead to increases in the water solubility of the emitted cadmium. Other reactions such as the formation of carbonate salts from cadmium oxide may also occur.

Cadmium is removed from the atmosphere through physical processes. Both wet and dry deposition have been judged to be significant. A number of deposition models have been proposed for atmospheric particles, and a wide range of cadmium deposition velocities has been measured or predicted.

General population exposure to atmospheric cadmium was estimated using data on cadmium concentrations throughout the state determined for the first six months of 1985. Review of other data, both from California and elsewhere, suggests that concentration averages calculated using data from the first six months of the year are reasonably representative of annual averages. Data from 21 sites in six air basins were used to calculate population-weighted estimates of exposure. We estimate that 10 million people are exposed to an average cadmium concentration of between 1.0 and 2.5 ng/m^3, of which one million people are exposed to an average cadmium concentration of between 1.8 and 5.6 ng/m^3.

Neither size distribution nor the compound forms of cadmium were determined in the ARB's measurements. Work done by others on the size

distribution of atmospheric cadmium indicates that atmospheric cadmium occurs principally on the surface of respirable particles (those less than 2.5 um in diameter). An average mass median diameter of 0.84 um has been calculated for atmospheric cadmium from ambient air measurements including data from an urban site in California. Although the compound forms of atmospheric cadmium have not been determined, it is known that atmospheric cadmium (in California and elsewhere) is 60-80 percent water soluble. Based on the possible compounds that could be present, we conclude that most atmospheric cadmium exists as the soluble sulfate form, with the insoluble oxide and carbonate salts comprising the rest.

To estimate exposure to atmospheric cadmium near sources, ARB staff used an air quality model to calculate the ambient concentration of atmospheric cadmium due to emissions from three secondary copper smelters in the South Coast Air Basin. These emissions were estimated to result in annual average exposure to atmospheric cadmium of up to 40 ng/m^3 for a population of 57,000 and up to 14 ng/m^3 for a population of 285,000.

Concentrations of cadmium measured in the atmosphere are much lower than those which are associated with chronic adverse health effects in occupational settings or which have produced acute effects in animal experiments. Because of this, and because cadmium is thought to exhibit a threshold effect for non-cancer health effects, we do not expect adverse health effects other than cancer to occur due to inhalation of cadmium at current or anticipated atmospheric concentrations.

Two separate cancer risk assessments were developed, both of which assumed that cadmium's carcinogenicity operates through a nonthreshold mechanism. One was based on a mortality study of workers in a cadmium

production plant. A direct linear model that incorporated an adjustment for the "healthy worker effect" was fitted to the exposure data and corresponding standardized mortality ratios for respiratory cancer. For exposure to 1 ng/m^3 cadmium, a best estimate of excess lifetime cancer risk of 2 per million and an upper 95% confidence limit (UCL) of 12 per million, were derived. The other cancer risk assessment was based on rat lung tumor incidence in a 31-month inhalation bioassay of soluble cadmium chloride aerosol. Application of the multistage model to these data yielded excess lifetime cancer risk estimates of 110 per million (maximum likelihood estimate) and 180 per million (upper 95% confidence limit) for exposure to 1 ng/m^3 cadmium.

Considering the degree of uncertainty associated with extrapolation of three to four orders of magnitude, the differences between the two risk assessments are relatively small. Nevertheless, the ranges of risk provided by these two sources of data do not overlap. Because the human data for exposure and for response were not found to have any major deficiencies, and because a conservative linear extrapolation was used, DHS staff has determined that reliance on the human-based risk assessment is unlikely to underestimate risk. The range of recommended risk estimates is therefore provided by the human-based risk assessment. Therefore, the excess lifetime cancer risk used in this report is 2 to 12 per million persons exposed throughout their lives to one ng/m^3 cadmium.

Exposures to cadmium via routes other than inhalation of ambient air were not considered in this risk assessment. The major nonoccupational exposure to cadmium is through food and smoking. Intake of cadmium from food and water has been estimated at 39 ug/day. While the bulk of human intake is via

ingestion, this route has not been associated with an increased risk of cancer either in humans or in experimental animals. Cadmium intake from smoking 20 cigarettes per day has been estimated at 2 to 4 ug/day. Typical daily exposure to cadmium from ambient air (not in close proximity to sources) may range from less than 0.02 ug/day to 0.10 ug/day. Occupational exposure, primarily through inhalation of airborne cadmium, is the greatest source of exposure for the cadmium worker population.

DHS staff emphasizes that the risk estimates derived in conducting a risk assessment are not exact predictions, but rather represent best estimates based on current scientific knowledge and methods. Uncertainty in this risk assessment stems from: (1) limitations in the data on which the assessment was based, (2) an extrapolation from occupational exposure levels to current ambient cadmium concentrations ranging over three to four orders of magnitude, (3) generalization from the mortality experience of adult white males in Colorado to the general population in California, (4) possible differences between occupational and nonoccupational exposures in terms of particle size distribution, and (5) potential inaccuracy and variability of ambient exposure measurements.

The DHS staff has determined that the possible roles of chance, bias and confounding factors in distorting the true dose-response relationship in the occupational study were likely to have been small. The DHS staff has also concluded that inaccuracies in the evaluation of exposure and cancer mortality in that study were likely to have been small. In addition, the net direction of these potential errors was likely to result in an overestimate of cadmium's carcinogenic potency. For these reasons, the DHS staff believes that the use of these epidemiologic data in a quantitative risk assessment is appropriate.

Furthermore, the use of human data eliminates uncertainty arising from interspecies extrapolation. Since the occupational exposures were by inhalation, there is also no extrapolation between routes of exposure. Therefore the DHS staff recommends that the range of risks for ambient exposures to cadmium be based on the best estimate and upper 95% confidence limit predicted from fitting a linear model to the human data. The hazard posed by atmospheric cadmium to residents of California was estimated by applying the risk estimate to cadmium concentrations measured in the state. Noncancer health effects are not expected to occur at concentrations of cadmium measured in populated areas of the state (long-term averages ranging from 1 to 2.5 ng/m^3). The range of estimated excess lifetime cancer risks from 24-hour-per-day exposure for a lifetime to average ambient airborne concentrations, estimated to be 1 to 2.5 ng/m^3, is 2 to 30 per million persons exposed. For people near emission sources of cadmium, the range of estimated excess lifetime cancer risks from 24-hour-per-day exposure for a lifetime to an average of 40 ng/m^3 of cadmium is 80 to 480 per million persons exposed. Based on air quality modeling of three sources of cadmium emissions, the ARB staff has estimated that approximately 57,000 people may be exposed to this concentration.

Based on the finding of cadmium-induced carcinogenicity and the result of the risk assessment, DHS staff finds that ambient cadmium is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

Based on interpretation of the available scientific evidence, ARB staff concludes that cadmium meets the definition of a toxic air contaminant, and recommends that it be listed as such. In making this recommendation, the ARB staff is unable to, based on available scientific information, identify a level below which adverse health effects are not anticipated to occur, and is therefore unable to recommend a threshold level.

II. EVALUATION OF CADMIUM

Cadmium is a rare element, making up on the average between one and two parts in ten million of the earth's crust. It is found in oil and coal at higher concentrations than are normally found in the earth's crust; it is also a contaminant of zinc and copper ores, from which it is recovered commercially.

Cadmium is used in a wide range of industrial applications. Cadmium metal is used as a component of certain alloys, as a corrosion inhibiting coating, and in certain types of electrical storage batteries. Its compounds are used as pigments and stabilizers, and in semiconductor manufacturing.

This wide usage of cadmium and its compounds, its presence as a natural contaminant in fossil fuels, other metals, and industrial raw materials, along with its high volatility relative to other metals, create a high potential for release of cadmium to the atmosphere. We estimate that between 16 and 18 tons of cadmium are emitted yearly into the State's atmosphere.

Exposure

Atmospheric cadmium concentrations were measured by the ARB in urban areas of the state during 1985. High-volume (hi-vol) samplers were used to collect 24-hour samples of particulate matter of 50 micrometer and smaller diameter; atomic absorption spectrophotometry was used to determine cadmium in the acid-soluble fraction of each sample.

Data are available for the first six months of 1985 from 21 sampling sites; these data were used to estimate exposure to atmospheric cadmium in the six areas in which the samplers were located. Data on atmospheric cadmium concentrations in California collected by the U.S. EPA in 1977, and information on seasonal variation of atmospheric cadmium in England suggest that January through June averages may be representative of annual averages.

Exposures in the San Francisco Bay Area and the South Coast air basins were calculated by interpolating site values to census tract centroids, yielding population-weighted averages. Exposures in the San Joaquin Valley, San Diego, and South Central Coast air basins, and in Sacramento County, were estimated by assuming the population in each area was exposed to the arithmetic mean concentration from sampling sites in that area. Values below the limit of detection (LOD) (1.0 ng/m^3) were found in one-half of the samples. To provide a range of average concentrations, we developed two treatments for values below the LOD which are referred to below as "zero values": a minimum average estimate was calculated assuming values below the LOD equal zero; a maximum average estimate was calculated assuming values below the LOD equal the LOD. Table I presents these exposure estimates.

TABLE I

Atmospheric Cadmium Exposure Estimates
Based on Zero Value Treatments
(Jan - June 1985 data)

Air Basin/Area	Range of Average Cadmium Concentration (ng/m^3) min.	max.	Exposed Population (millions)
San Francisco Bay Area	2.3	2.5	4.34
South Coast	1.3	1.8	10.1
San Joaquin Valley	0.7	1.3	2.31
San Diego	0.8	1.0	2.13
South Central Coast	0.5	1.0	1.12
Sacramento (County)	0.3	1.0	0.89
All areas	1.3	1.8	21

The range of exposure estimates provided by different treatment of zero values does not reflect uncertainty resulting from the small number of samples collected at each site (n = 10 to 36) or from variance in measurements. To better estimate exposure, we calculated 95 percent confidence intervals for

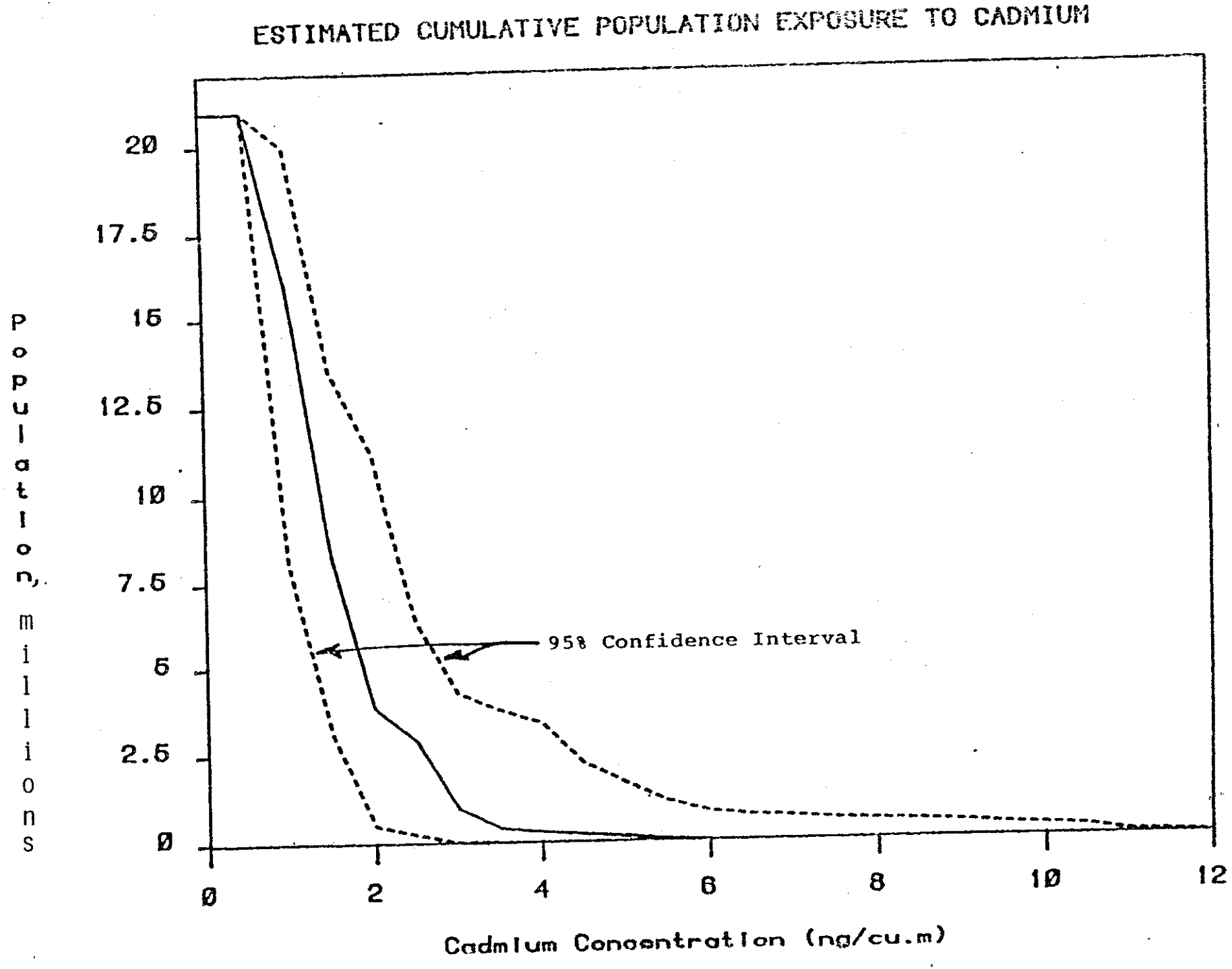
the mean concentration at each site. These confidence intervals reflect uncertainty due to sample size and the accuracy of the measurement method, in addition to the uncertainty from values below the detection limit. The estimated 95 percent confidence intervals for the average cadmium concentrations in the areas studied are given in Table II.

TABLE II

Atmospheric Cadmium Exposure Estimates
95% Confidence Intervals
(Jan - June 1985 data)

Air Basin/Area	95% Confidence Limits of Average Cadmium Concentration (ng/m^3) Lower	Upper	Population (millions)
San Francisco Bay Area	1.5	4.7	4.34
South Coast	1.0	2.3	10.1
San Joaquin Valley	0.7	1.5	2.31
San Diego	0.6	1.2	2.13
South Central Coast	0.5	1.0	1.12
Sacramento (County)	0.5	0.9	0.89
All areas	1.0	2.5	21

Comparison of the estimated ranges in average concentration shows that uncertainty from values below the detection limit is small compared to the 95% confidence intervals, except when averages are near the LOD, when both methods give comparable ranges. Figure 1 shows cadmium concentrations plotted against cumulative population for the mean and the upper and lower 95 percent confidence limits. We estimate that approximately 10 million people (50 percent of the population in the areas studied) are exposed to at least 1.5 ng/m^3 cadmium (range: 1.0 - 2.5 ng/m^3), and that approximately one million people (five percent of the population in the areas studied) are exposed to at least 3.5 ng/m^3 cadmium (range: 1.8 - 5.6 ng/m^3). The exposures discussed here are based on cadmium measured on particles 50


ESTIMATED CUMULATIVE POPULATION EXPOSURE TO CADMIUM
Population, millions
20
17.5
15
12.5
10
7.5
5
2.5
0
95% Confidence Interval
0
2
4
6
8
10
12
Cadmium Concentration (ng/cu.m)

micrometers (um) and smaller in diameter; the fraction of cadmium on respirable particles (less than 2.5 um diameter) was not determined. The size distribution of cadmium on atmospheric particles has been found by others to be bimodal; the larger peak is seen at 0.3 - 1 um, with a smaller peak at 3 - 10 um. This tendency is observed among studies which differed in sampling location (industrial, urban, and remote/background), year (1965 - 1979), and measurement method. Milford and Davidson (1985) calculated an average particulate cadmium mass median diameter of 0.84 um from particle size distributions in 14 studies of industrial, urban, and remote areas, including an urban area in California.

Data used to assess atmospheric cadmium exposure reflect total or acid extractable cadmium. The probable compounds of cadmium occurring in atmospheric particulate matter can be inferred from data on the solubilities of atmospheric cadmium particles, the combustion chemistry of major sources, and the solubilities of cadmium salts. Analyses of emitted particulate from fossil fuel fired boilers, and from a primary copper smelter, indicate that metals are emitted principally as the sulfate, and to a lesser extent as the oxide or carbonate. This is consistent with the observed water solubilities of cadmium aerosols in California (84 percent of cadmium particulate matter collected at an urban costal location was water soluble), and elsewhere (74 percent of continental aerosol collected in rural Tennessee was water soluble).

Sources and Fate

Although cadmium occurs as a trace element of crustal materials, comparisons of the compositions of atmospheric particulate matter and crustal materials strongly suggests that atmospheric cadmium originates mainly from

high temperature industrial processes. The ratio of the cadmium to aluminum concentration ratio in air to their ratio in crustal materials is defined as the enrichment factor (EF) for cadmium. EF values less than 5 are generally considered to be indicative of a crustal or soil source; higher values of EF are suggestive of sources causing enrichment in cadmium, i.e., high temperature sources (combustion or pyrometallurgical). An average EF of 1,900 for cadmium at urban, rural, and remote sites in the U.S. and elsewhere has been reported. No California-specific data are available, but the enrichment phenomenon observed elsewhere supports the supposition that atmospheric cadmium in California is emitted principally from high temperature industrial sources.

An inventory of cadmium emissions in the state indicates that most (about 90 percent) cadmium is emitted from high temperature processes. These sources have been shown to emit cadmium on particulate matter principally less than 2 um in diameter, with typical mass median diameters of 1 um. The enrichment of cadmium on smaller diameter particles has been attributed to condensation of cadmium (volatilized during combustion) on the surface of emitted particles as cooling of combustion gases occurs. Because small particles have greater surface to mass ratios than large particles, the concentration of cadmium on a mass basis is greater for small particles.

Cadmium is emitted from a number of different sources. Approximately 80% of the cadmium accounted for in a statewide emission inventory was from stationary sources with the balance emitted by motor vehicles.

Stationary sources of cadmium emissions include secondary smelters, cement manufacturing plants, cadmium electroplating facilities, sewage sludge

incinerators, and industrial, commercial, and utility plants where coal or oil is burned.

Cadmium is also emitted from mobile sources. Cadmium is a component of diesel fuel and gasoline, and is emitted when these are burned. Also, cadmium is present in vehicle tires and consequently in the particles resulting from tire wear. Table III gives a summary of ARB statewide emission estimates for cadmium.

TABLE III

Statewide Cadmium Emissions

Stationary Sources	Inventory Year	Estimated Statewide Emissions (tons/yr.)
Secondary Smelters	1981	8.5
Cement Manufacturing	1984	0.02-1.1
Oil Combustion	1983	3-4
Coal Combustion	1981	0.2
Cadmium Plating	1982	0.6
Sewage Sludge Incineration	1982	0.4
Total Stationary Sources		13-15
Mobile Sources		
Motor Vehicle Fuel Combustion	1984	1.7
Vehicle Tire Wear	1984	0.9
Total Mobile Sources		2.6
Total All Sources		16 - 18

There is evidence of atmospheric reactions of cadmium emitted from coal combustion. An increase in the solubility of cadmium on coal fly ash has been attributed to reaction of emitted cadmium oxide in the plume to form cadmium sulfate, phosphate, or fluoride. In addition to this group of reactions,

which would account for observed increases in the solubility of emitted cadmium, the reaction of metal oxides in fly ash with carbon dioxide to form metal carbonates has been observed. If this reaction occurs with cadmium, it would not affect the solubility of atmospheric cadmium directly, because both the oxide and carbonate salts of cadmium are insoluble.

Cadmium is removed from the atmosphere through both wet and dry deposition. The rates of trace metal deposition are believed to depend on meteorology, vegetation (canopy) characterisitics, and differences in local or regional emissions.

Non-Cancer Health Effects

Cadmium has been found to induce a number of noncarcinogenic toxic effects in experimental animals and humans. Cadmium has moderate acute toxicity, producing gastrointestinal or pulmonary effects from ingestion or inhalation, respectively. Chronic and subchronic exposures to cadmium have been associated with a wide range of adverse outcomes that include cardiovascular, endocrine, hepatic, bone, hematological, immunological, respiratory, renal, reproductive, and teratogenic effects. DHS staff has concluded that renal toxicity is the most sensitive noncarcinogenic effect, in that it has been reported to occur at lower exposure levels than other effects.

The staff of the Air Resources Board has estimated that long-term atmospheric concentrations of cadmium in California are in the range of less than 1, to 6 ng/m^3. A daily retention rate of cadmium estimated to induce renal toxicity in 10 percent of the population has been estimated to be 6.6 to 24.6 ug/day over a 50-year period. Ambient air concentrations necessary to attain this range of retention rates have been estimated to be 650 to 2500 ng/m^3, assuming 50 percent pulmonary absorption. Although no threshold

exposure level has been determined for renal toxicity, the staff of DHS believes that such a level does exist. The staff of DHS has concluded that the two to three orders of magnitude difference between the estimated atmospheric concentrations of cadmium and those concentrations necessary to attain a retention rate at which 10 percent of the population would develop renal toxicity is sufficiently large that atmospheric cadmium does not pose a significant hazard for renal toxicity. Since renal toxicity is the most sensitive noncarcinogenic endpoint, any other acute or chronic noncarcinogenic toxic effects from current ambient levels are not expected.

Carcinogenic Effects

Cadmium has induced cancer in experimental animals and has been associated with an increase in human cancers in epidemiological studies. Cadmium has produced injection site tumors (in rats) and remote tumors (in rats and mice) following subcutaneous or intramuscular injections, and has produced lung tumors in rats exposed to cadmium chloride aerosol. Several studies in which cadmium was given by the oral route have been negative, perhaps because of poor gastrointestinal absorption and low susceptibility of gastrointestinal epithelial tissue to carcinogenesis induced by cadmium. The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of carcinogenicity in animals and that, for practical purposes, cadmium should be regarded as if it presents a carcinogenic risk to humans. DHS staff concurs in these conclusions.

Epidemiological evidence has suggested an association between cadmium exposure and neoplasia, including respiratory, renal, prostatic, and bladder cancers. For the latter three cancers, the evidence is suggestive or inconclusive; however, there is strong evidence of an association between

cadmium exposure and an increased risk of respiratory cancer. Several occupational studies have shown some association between cadmium exposure or potential exposure and lung cancer. A recently published, well-designed study which evaluated a cohort of cadmium-exposed workers found a highly statistically significant dose-response relationship. Neither bias nor confounding appeared to be responsible for the observed excess lung cancer risk.

A variety of studies have indicated that cadmium is mutagenic and clastogenic. However, a number of similar studies have given negative results. The staff of DHS has concluded that there is only limited evidence that cadmium is mutagenic and clastogenic.

There is also evidence that cadmium can bind to DNA and cause mispairing of synthetic polynucleotides. This type of activity may cause a mutagenic or carcinogenic effect. The mechanism of action for this type of effect is believed to have no threshold associated with it. In the absence of compelling evidence of a threshold, the staff of DHS considers the mechanism of cadmium carcinogenesis to be a nonthreshold process.

Risk Due To Atmospheric Cadmium

At ambient concentrations, cadmium was estimated to present a potential carcinogenic risk to humans. This conclusion was based on two separate risk assessments, one utilizing animal data, the other utilizing human data.

In a 31-month inhalation bioassay, rats were exposed to cadmium chloride aerosol at concentrations of 0, 2.2, 4.1 and 8.3 ug/m^3 pure cadmium. The tumor incidence rates for these four dose groups were, respectively, 0%, 15%, 53% and 71%. Several models were fit to these data. The most health-conservative extrapolation was achieved by fitting the multistage

model, which predicted an excess lifetime cancer risk of 110 per million persons continuously inhaling 1 ng/m^3 cadmium in ambient air throughout their lives. The upper 95% confidence limit for this risk estimate was 180 per million persons.

The human data used for a risk assessment was based on an occupational cohort study of 585 workers exposed to cadmium in a production plant. Based on cumulative exposures, the follow-up years for these workers were divided into 3 exposure categories. At median cumulative doses of 184, 796 and 2762 ug/m^3 of cadmium, standardized mortality ratios (SMRs) of 53, 152 and 280 were observed. A linear excess relative risk model with an adjustment for the healthy worker effect was fitted to these data by an iterative least squares algorithm. The model predicted an excess lifetime cancer risk of 2 per million persons inhaling 1 ng/m^3 cadmium in ambient air throughout their lives. The upper 95% confidence limit for this risk estimate was 12 per million.

The upper 95% confidence limit for lifetime cancer risk based on the rat study was about 15 times the upper 95% confidence limit of risk predicted by the epidemiological study. The maximum likelihood estimate from the animal data is about 10 times the upper 95% human-based estimate. Members of the DHS staff have concluded that the human-based quantitative risk assessment is sufficiently health conservative because: (1) it is based on a linear extrapolation, (2) potential inaccuracies in the human data regarding exposure or response are likely to be small, and (3) the net direction of these inaccuracies are likely to result in an overestimate of potency. Therefore, the DHS staff believes that the human-based risk assessment provides the most appropriate range of risks. The range of estimated excess lifetime cancer

risks from 24-hour-per-day exposure for a lifetime to atmospheric concentrations of cadmium (1 to 2.5 ng/m^3) is therefore 2 to 30 per million persons exposed. In the vicinity of sources of cadmium emissions, ambient exposures may reach an annual average of 40 ng/m^3, with the estimated excess lifetime cancer risk being 80 to 480 per million persons exposed.

III. ENVIRONMENTAL IMPACTS

The identification of cadmium as a toxic air contaminant is not in itself expected to result in any environmental effects. The identification of cadmium as a toxic air contaminant by the Board may result in the Board and air pollution control districts adopting toxic control measures in accordance with the provisions of state law. Any such toxic control measures may result in reduced emissions of cadmium to the atmosphere, resulting in reduced ambient concentrations, concurrently reducing the health risk due to cadmium. Therefore, the identification of cadmium as a toxic air contaminant may ultimately result in environmental benefits. Environmental impacts identified with respect to specific control measures will be included in the consideration of such control measures pursuant to Health and Safety Code Sections 39665 and 39666.

IV. REGULATORY BACKGROUND AND PROCEDURES

Division 26, Chapter 3.5 of the Health and Safety Code** (HSC) and Food and Agriculture Section 14021 et seq. set forth the procedure for identifying and controlling toxic air contaminants in California. (These provisions were enacted in September 1983 as Assembly Bill 1807, Stats. 1983, ch. 1047.) The Department of Food and Agriculture is responsible for identifying and controlling TACs in their pesticidal uses. The ARB has authority over TACs in all other uses.

** Health and Safety Code Section 39650; all statutory references are to the Health and Safety Code, except as otherwise stated.

HSC Section 39650 sets forth the Legislature's findings about substances which may be TACs. The Legislature has declared:

> "That public health, safety, and welfare may be endangered by the emission into the ambient air of substances which are determined to be carcinogenic, teratogenic, mutagenic, or otherwise toxic or injurious to humans."

The findings also include directives on the consideration of scientific evidence and the basis for regulatory action. With respect to the control of TACs, the Legislature has declared:

> "That it is the public policy of this state that emissions of toxic air contaminants should be controlled to levels which prevent harm to the public health."

The Legislature has further declared that, "while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health."

In the evaluation of substances, the Legislature has declared that the best available scientific evidence, gathered from both public agencies and private sources including industry, should be used. The Legislature has also determined that this information should be reviewed by a scientific review panel and by the public.

The Board's determination of whether or not a substance is a toxic air contaminant includes several steps specified by the HSC. First, we request the DHS to evaluate the health effects of a substance (Section 39660). The evaluation includes a comprehensive review of all available scientific data. Upon receipt of a report on health effects from DHS and in consideration of

their recommendations, we prepare and submit a report to the Scientific Review Panel (SRP) for its review (Section 39661). The report consists of the DHS report (Part B), material prepared by the ARB staff on the use, emissions and ambient concentrations of the substance (Part A), and public comments on the draft report and responses (Part C). It serves as the basis for future regulatory action by the Board. The report is also made available to the public, which may submit comments on the report.

After receiving the SRP's written findings on the report, the Board issues a public hearing notice and a proposed regulation identifying the substance as a toxic air contaminant. If, after a public hearing and other procedures to comply with Government Code Section 11340 et seq., the Board determines that a substance is a toxic air contaminant, its findings must be set forth in a regulation (Section 39662). The HSC also sets forth procedures for developing and adopting control measures for substances identified as TACs (Sections 39665-39667).

TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CADMIUM

PART A - PUBLIC EXPOSURE TO, AND SOURCES OF, ATMOSPHERIC CADMIUM IN CALIFORNIA

Prepared by the Staff of
the Air Resources Board

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December 1986

Technical Support Document

Report to the Air Resources Board on Cadmium
Part A - Public Exposure to, and Sources of, Atmospheric Cadmium in California

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I. INTRODUCTION

Cadmium and its compounds are significant from both a commercial and an environmental perspective. Cadmium or its compounds is used to inhibit corrosion of other metals, to color and to stablize plastics, and to achieve a number of other unique or beneficial properties in industrial and commercial applications.

Cadmium is present at trace levels in fossil fuels and some metal ores. Because cadmium is volatile (relative to other metals), there is a high potential for its release to the atmosphere during ore smelting of some metals and during fossil fuel or waste combustion. Cadmium may also be emitted to the atmosphere during its direct industrial use. Cadmium has been measured in the atmosphere of California, both in special studies and on an ongoing basis, for more than thirty years.

This report presents statewide estimates of present and future usage and emissions of cadmium, a discussion of the available information on the nature and fate of that emitted cadmium, and an estimate of exposure to atmospheric cadmium for both the general public and for people living close to major sources of cadmium emissions. In discussion of each of these topics areas of incomplete knowledge are identified, and, where possible, inferences are drawn using available information.

II. PROPERTIES

Cadmium is a soft, silver-white metal which is found as the sulfide at trace concentrations in the earth's crust. In its elemental form, cadmium is resistant to corrosion by alkalies and salt water, and retains its metallic luster in air. The molecular weight of metallic cadmium is 112.4, and its boiling point is 767°C. The relatively high volatility of cadmium and some of its compounds compared to other metals is significant from an air pollution standpoint; cadmium vaporized during combustion or other high temperature processes, condenses on particles as the gas cools. Preferential enrichment of cadmium on fine particles (less than 2 micrometers) occurs as a result. Because some air pollution control devices have lower removal efficiencies for small particles than for large, cadmium is emitted predominantly on small particles, which are respirable.

The most common oxidation state of cadmium is +2, although there are a small number of compounds in which cadmium occurs in the +1 oxidation state (Hollander and Carapella, 1978). Commercially and environmentally significant compounds of cadmium exhibit a wide range of properties; selected properties of several compounds are given in Table II-1.

TABLE II-1

Physical Properties of Selected Cadmium Compounds

Species	Molecular Weight	Solubility[1] Water	Acid	Boiling Point (°C)
Cadmium	112.4	i	s	767
acetate	230.5	s	s	decomposes
carbonate	172.4	i	s	decomposes
chloride	183.3	s	s	960
fluoride	150.4	s	s	1758
oxide	128.4	i	s	1559
orthophosphate	527.1	i	s	---
sulfate	208.5	s	s	----
sulfide	144.5	i	s	980 (sub. in N_2)

Sources: IARC, 1976; Hollander and Carapella 1978; Weast, 1973, Germani, et al, 1981

1) i = insoluble
s = soluble

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III. SOURCES AND FATE OF ATMOSPHERIC CADMIUM

A. Production and Usage

Cadmium is a rare element, found mainly as a sulfide in ores of zinc, copper, and lead. Because of its rarity, because it occurs with metals of economic importance and because it can be recovered during the refining of these other metals, cadmium is not mined separately; it is always a byproduct of other mining operations. It is most commonly produced commercially as a by-product of zinc (and to a lesser extent, copper and lead) smelting and refining. During 1984, five plants in the United States produced cadmium metal from zinc ores; none of these were located in California (U.S. Department of Interior [DOI], 1985a).

Cadmium consumption in the United States during 1984 has been estimated to be 4,200 tons. Domestic production of cadmium during 1984 was 1,800 tons (48 percent of consumption), with imports and reserves making up the difference. During the period 1973 to 1984, approximately 58 percent of cadmium consumed in the United States was imported, mainly from Canada, Australia, Peru, and Mexico (U.S. DOI, 1983; U.S. DOI, 1985a,b).

Historical national production, importation, and consumption estimates are given in Figure III-1. The U.S. Department of the Interior has forecast an annual increase in cadmium consumption of approximately 1.9 percent during the period 1983-2000 (U.S. DOI, 1985a).

Figure III-2 depicts the national demand for cadmium in 1984 by major use category. The main user of cadmium (as cadmium chemicals) is the plating industry. Cadmium plating provides excellent protection for iron, steel, brass and aluminum against corrosion, especially in marine and alkaline environments. Historically, 37 percent of cadmium consumption in the United

Figure III-1

National Cadmium Production, Imports and Consumption

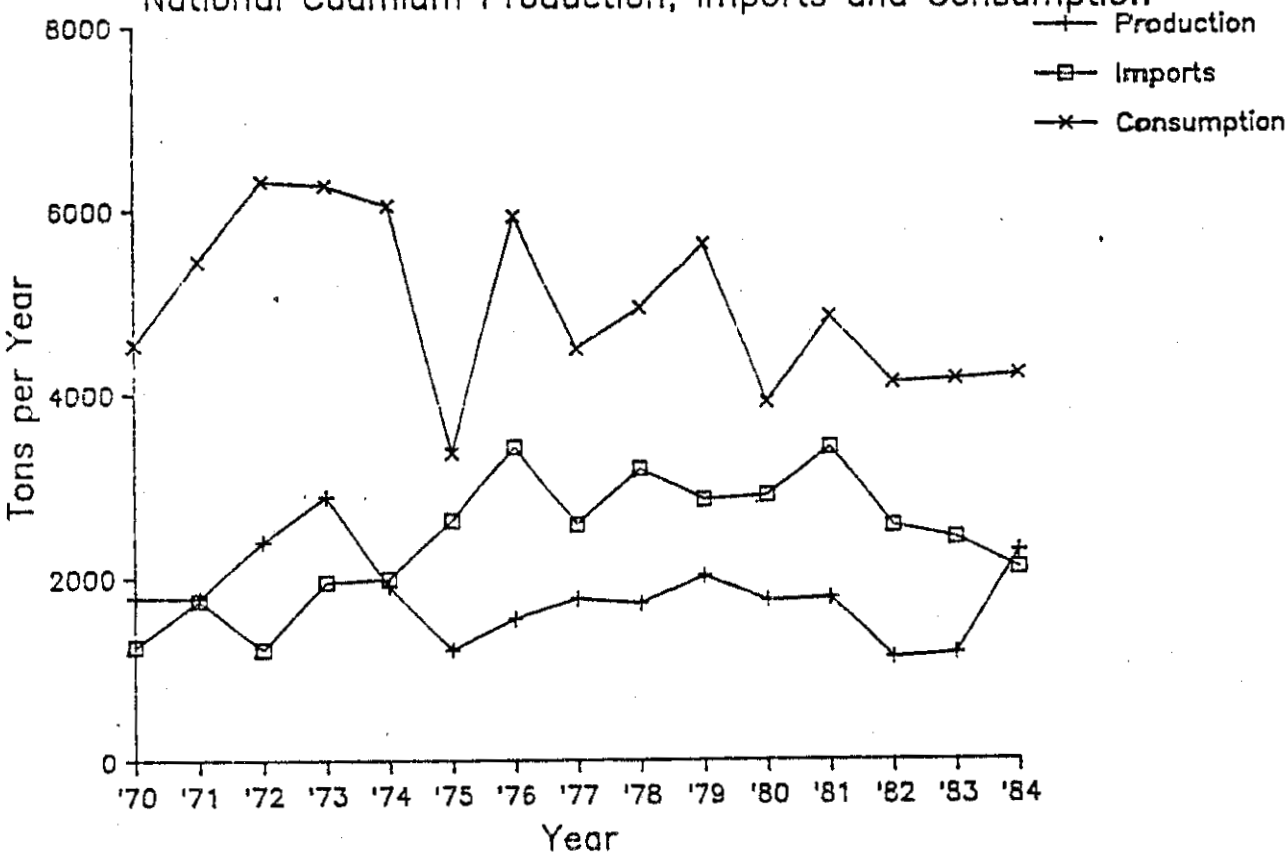
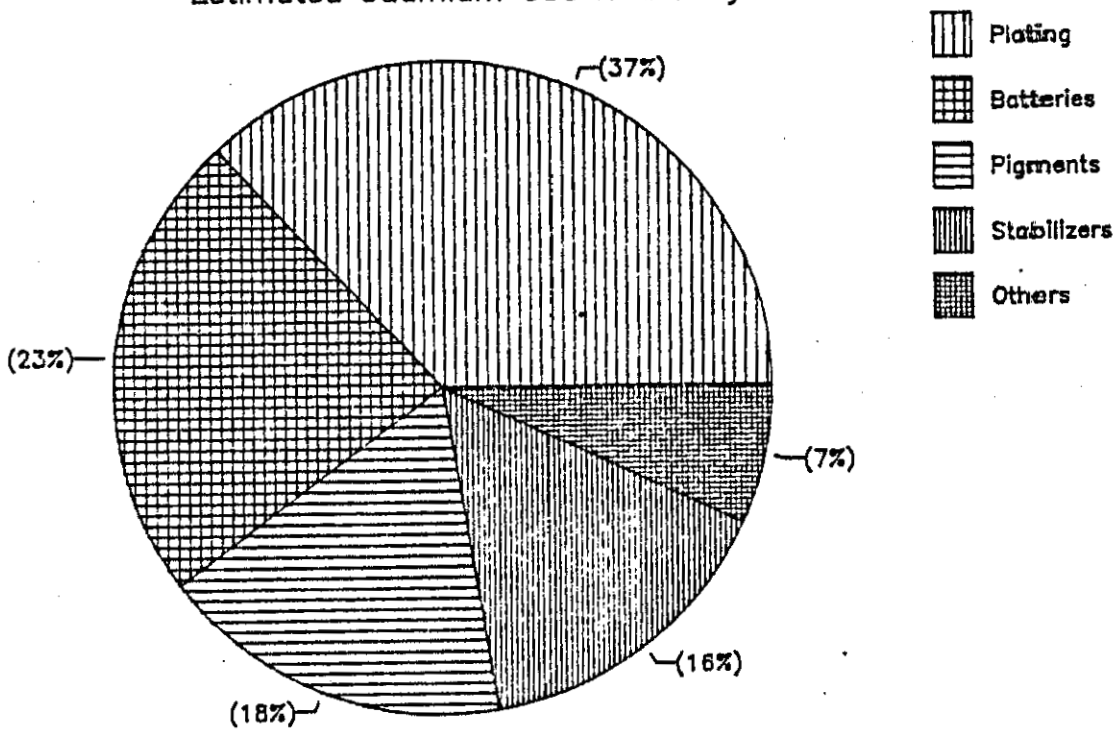


Figure III-2

Estimated Cadmium Use Nationally In 1984



States was for plating, which yields an estimate of 1,550 tons in 1984 (U.S. DOI, 1985a and 1985b; CARB, 1985a). The number of cadmium platers in California is not known; however, 31 cadmium platers have been listed in the South Coast Air Quality Management District (SCAQMD) inventory of potentially toxic chemicals (Zwiacher et al., 1983).

Cadmium is also used extensively by the battery industry to produce nickel-cadmium, silver-cadmium and mercury-cadmium batteries. Nickel-cadmium batteries are commonly used in aircraft, alarm systems, cameras, calculators, etc. (U.S. DOI, 1985a). There are no nickel-cadmium battery manufacturers in California.

Cadmium pigment and stabilizer production accounted for consumption of 1,390 tons of cadmium nationally in 1984 (U.S. DOI, 1985b and CARB, 1985a). Cadmium sulfide and sulfoselenide are the most important compounds used in pigments. High temperature stability, brilliant colors, high opacity, and resistance to chemical attack and degradation by light are characteristics of cadmium pigments. Cadmium compounds are used as stabilizing agents in many polyvinyl chloride products such as clear sheet, film and tubing, and cushioned floor covering.

Cadmium and its compounds are employed in a variety of other uses. Cadmium sulfide and cadmium telluride are used in the electronics industry to produce photocells and light emitting diodes. Cadmium metal alloyed with copper is used in the production of automobile radiators. In tires, cadmium sulfide is used as a curing agent. Cadmium salts such as cadmium sebacate, are used in fungicides, and cadmium phosphate is used in fertilizers (Anderson, 1973; Tierney et al., 1979). The cadmium content of American phosphatic fertilizers range from 3.48 to 156 ppm (Hammons et al., 1979).

B. Sources of Current and Projected Cadmium Emissions

Approximately 90 percent of cadmium emission in California are the result of either the combustion of fuels or the smelting of metals which contain cadmium as a trace contaminant. Because of cadmium's high volatility relative to other metals, cadmium is vaporized by high-temperature processes and then condenses on the surface of particles in the gas stream. Because it is deposited uniformly on the surface of all particles, small particles with a larger surface area to volume ratio are found to contain higher concentrations of cadmium. For many types of sources significant in California, cadmium has been determined to occur on particles mostly 2 um in diameter or smaller (Milford and Davidson, 1985; Davison, et al., 1974). Available information suggests that cadmium is emitted from these source types principally as oxide and sulfate compounds, and also possibly as fluoride, chloride, and phosphate compounds.

The remaining 10 percent of cadmium emitted in the state is from either low-temperature sources such as cement manufacturing and tire wear, or from direct emission of cadmium compounds from cadmium plating operations.

Table III-1 summarizes statewide cadmium emissions.

Stationary Source Emissions

Although electroplating represents the largest use of cadmium, estimated emissions from cadmium plating in California are less than three percent of estimated total emissions. Most cadmium plating operations use cadmium-cyanide baths (Davis, 1970 and Graham, 1971), which are made up of cadmium

Table III-1

Estimated Cadmium Emissions in California

Source	Source Type	Emissions (tons/year)	Inventory Year	Reference
Secondary Smelters				
Copper	Area	8.1	1981	9,17
Steel Mills	Area	0.1	1981	9,17
Zinc	Area	0.3	1981	9,17
Fuel Combustion				
Coal	Point	0.2	1981	24,32
Distillate Oil	Area	0.6	1983	5,11,30
Residual Oil	Area	1.5-3.1	1984	1,4,5,6
Diesel	Area	0.4	1984	1,4,18
Waste Oil	Area	0.1	1983	6,10,28
Cement Manufacturing	Point	0.02-1.1	1984	5,6,7,8
Cadmium Plating	Area	0.6	1982	41
Sewage Sludge Incinerators	Area	0.4	1982	3,8,22
Motor Vehicles				
Fuel Combustion	Area	1.7	1984	5,26,36
Tire Wear	Area	0.9	1984	4,26,36

oxide or cadmium cyanide and sodium cyanide. During the plating process electric energy decomposes water in the bath, evolving hydrogen and oxygen gases; these gases carry cadmium in the plating bath to the surface of the bath and cause it to be entrained with the gases and emitted to the atmosphere. If the efficiency of the plating process is low, gassing will be high and cadmium emissions from plating process will also be high. Based on the South Coast AQMD survey (Zwiacher, et al., 1983), and assuming the distribution of cadmium platers is similar to chromium platers, it is estimated that approximately 80 cadmium platers operate in California. Cadmium emissions from this source are estimated to have been 0.6 ton in 1982 (see Appendix C for calculation).

Fuel combustion at stationary sources is responsible for approximately 3-4 tons of airborne cadmium per year. Residual oil combustion is the largest source of cadmium emissions in this category and accounts for well over half of the estimated cadmium emissions from fuel combustion.

The largest source of cadmium emissions from fuel combustion is oil and gas production activities. Utilities account for 0.7% to 17% of cadmium emissions from fuel combustion with the remainder being divided among ships, chemical manufacturers, industrial boilers, and other fuel oil users. Waste oil also contains cadmium, concentrations of which have been measured at levels as high as 110 ppm (Franklin Associates, Ltd., 1983).

During combustion, the trace levels of cadmium in distillate, residual, diesel, and waste oil are emitted into the atmosphere. There is a large variation in the cadmium content of residual oil. Southern California Edison (SCE) sampled oil in 1986 at its power plants and reported an average of 0.01 ppm cadmium (Southern California Edison, 1986). PG&E sampled oils at its power plants and reported an average cadmium concentration of 0.39 ppm (range 0.31 ppm to 0.52 ppm) (Pacific Gas and Electric Co., 1986). Several documents (Menczel, et al., 1984; U.S. EPA, 1984; John J. Yates & Associates, 1983; Krishnan and Hellwig, 1982) indicated the cadmium concentration of residual oil to be as high as 1 ppm. Lower trace metal concentrations, specifically cadmium, in residual oil burned at power plants in the South Coast are attributed to the South Coast Rule 431.2 which limits the sulfur content of any liquid fuel burned at power plants and refineries to 0.25 percent (SCAQMD, undated).. This is half the 0.50 percent sulfur limit applied to liquid fuels burned in the Bay Area (BAAQMD, 1984). Staff have revised the estimated cadmium emissions from residual oil combustion based on cadmium content of fuel oil reported by SCE and PG&E (see Appendix C).

Residual fuel oil used by the California utilities has declined steadily since 1977, falling from 124 million barrels in 1977 to 4.5 million barrels in 1985 (CEC, 1986a; CEC, 1986b). In 1984, utilities used approximately 16 percent of all residual oil burned in the state (CARB, 1986a; CARB, 1986b). The California Energy Commission (CEC) forecasts a three-fold increase in residual oil use by the utility industry from 1985 to 1997 (CEC, 1986a; CEC, 1986b). By 2005, residual oil used by the utility industry would return to the 1984 level (CEC, 1986a). The use of residual oil in the industrial, commercial and transportation sectors is forecast to remain about the same through the year 2005 (CEC, 1986b). Because cadmium emissions from residual oil combustion is directly proportional to the amount used, cadmium emissions from residual oil combustion are therefore expected to increase in the next decade and then return to the 1984 level by 2005.

Cadmium emissions from coal combustion are expected to increase due to the increase in coal consumption by various industries. Five California cement plants have converted or plan to convert from a wet production process which uses natural gas as a fuel, to a more efficient dry process which often uses coal. Coal consumption from cement manufacturers will also rise due to the increase in their capacities. In 1984, 11 cement manufacturers in California produced 8.7 million tons of cement (U.S. DOI, 1985d) and consumed a total of approximately 1.6 million tons of coal. In 1985, the Department of the Interior forecast the U.S. cement production in 1990 and 2000 to be 77 million tons and 87 million tons, respectively (U.S. DOI, 1985c). Based on United States and California cement production data for 1980 through 1984, California produced an average of 11.2 percent of the cement production in the nation (U.S. DOI 1985c,d). Assuming the ratio of the California cement production to the United States is the same in the future, California cement

production is forecast to be approximately 8.6 million tons in 1990 and 9.7 million tons in the year 2000.

Approximately 0.17 ton of coal is required as fuel to produce 1.0 ton of cement. Assuming the recent degree of coal use continues into the future, the California cement industry is forecast to use approximately 1.5 million tons of coal in 1990 and 1.6 million tons in 2000.

Although a number of coal gasification programs have been or are being considered by the utility industry, only one plant is currently known to gasify coal in Southern California. This plant used 108,000 tons of coal from June 1984 through January 1985 (Wolk and Holt, 1985).

The compound form of cadmium emitted from fossil fuel combustion has not been determined. The general composition of particulate matter emitted from coal and oil combustion (fly ash) has been studied, and provides some insight into the possible compound forms of cadmium. Eatough, et al., (1981) reported sulfate to be essentially the only acid-extractable anion present in oil-fired power plant fly ash smaller than 3 um (chloride was present at 0.1 mole percent of sulfate). Henry and Knapp (1980) found that an average of 65 percent of oil combustion fly ash was water soluble; exclusive of carbon, an average of 86 percent of the fly ash was water soluble. Sulfate was the only anion found above trace values in the water soluble phase; metal oxides were determined to comprise the balance of the fly ash. The range of water solubility in six samples ranged from 23.3 to 98.5 percent, and the percentage of sulfate ranged from 12 to 58. This range of values is consistent with Dietz and Weiser's (1983) conclusion that metal sulfate emissions from oil-fired power plants are related to fuel composition (sulfur and vanadium concentration), combustion parameters (excess oxygen and temperature

in the combustion chamber), and air pollution control device type and performance.

Cadmium in fly ash emitted from coal combustion was determined by Hansen and Fisher (1980), and by Davidson, et al., (1974) to be concentrated at the surface of particles. Because the volatile non-metals have also been determined to occur on the surface of fly ash particles (Smith, 1981), Hansen et al., (1984) have postulated that cadmium may occur in coal fly ash as the fluoride, phosphate, or sulfate. The occurrence of these compounds on the particle surface is thought to depend on the concentration of the metal oxide at the particle surface, the concentrations of HF, SO_3, and P_4O_{10} in the flue gas, and the temperature and contact time of the particles and flue gas. Hansen and Fisher (1980) showed that 65 percent of acid-soluble cadmium on respirable fly ash from coal combustion was water soluble; this suggests that most cadmium occurs in the water-soluble sulfate, fluoride, or phosphate form, and that the balance is the acid-soluble oxide or carbonate form (Gendreau, et al., 1980).

The size distribution of cadmium on fossil-fuel combustion fly ash has been investigated by Davidson, et al., (1974), Jacko and Neuendorf (1977), Toca, et al., (1973), Hansen and Fisher (1980), and others. The common conclusion is that cadmium shows a pronounced concentration trend with particle size, occurring at increasing concentrations on smaller particles.

Emissions from secondary smelters result from cadmium present in scrap metal or feedstock. Cadmium is not recovered from these smelters, cadmium present in the feed materials which is not collected by air pollution control devices is released to the environment. Table III-1 lists cadmium emissions from secondary copper, steel and zinc smelters. Together, secondary smelters are estimated to have emitted 8.5 tons of cadmium in 1981.

The compound forms of cadmium emitted from primary smelters have been determined to be the sulfate and oxide forms (Eatough, et al., 1981; Radian, 1985). The extent to which cadmium would be emitted from secondary smelters as the sulfate would depend on the amount of sulfur present during smelting. We expect this to be much less in secondary than in primary smelting; therefore, we hypothesize that cadmium will be emitted from secondary smelting primarily as cadmium oxide, and to a lesser extent as cadmium sulfate.

Cadmium emitted from secondary smelters is expected to exhibit tendencies of surface enrichment, and therefore, a trend of increasing concentration on small particles. Jacko and Neuendorf (1977) showed that particles emitted from pyrometallurgical processes have mass median diameters of less than 1.0 um, and that a large percentage (30 to 50) of cadmium emitted from such processes is found on particles in the respirable range (less than 2.5 um diameter). This observation has been corroborated by Van Graen, et al., (1983), who concluded that surface enrichment of trace elements in particles from high temperature processes is universal, based on analysis of dust from an electric steel making furnace.

Of the secondary smelters, copper smelters are the largest source of cadmium emissions. Processes in secondary copper include: a) sweating scrap to remove low melting point metals or burning to remove insulation from copper wire; b) smelting and refining to obtain a certain type of copper; and c) alloying to modify the final product. No control devices are employed in wire burning; however, smelters and furnaces are usually equipped with hoods and baghouses (Coleman, 1970) to reduce direct cadmium emissions.

The ARB's Emissions Data System (EDS) includes 71 secondary copper smelters in California for inventory year 1981. Using an emission factor of 3 lb. Cd per ton of scrap and assuming 90 percent control, cadmium emissions

from copper smelters were estimated to be 8.1 tons in 1981 (Coleman, et al., 1979 and CARB, 1985d).

The production of secondary lead consists mainly of melting down lead batteries, lead oxide drosses, recycled dust and metal scrap in reverberatory or blast furnaces at 930 degrees C. Cadmium is released in this process (Anderson, 1973). Based on available data, the amount of cadmium emitted from secondary lead smelters in California is expected to be small.

Cadmium is present as an impurity in the material used to produce cement and is emitted during cement production. Currently, cement is produced by either a dry or a wet process. Particulate emissions, including cadmium, from these two processes differ primarily due to the nature of the processes involved. Cadmium emissions from cement production for both the dry and the wet process were estimated to be between 0.02 and 1.1 ton during 1981 (see Appendix C).

As the result of conversion from wet to dry processes in the cement industry and expected increases in the plants' capacities (Sierra Energy & Risk Assessment, Inc., 1982), cadmium emissions from cement manufacturing are expected to increase.

The estimate of cadmium emitted from sewage sludge incineration was based on the fraction of cadmium in the particulate matter and particulate matter emissions from municipal sewage sludge incinerators (Bennett, et al., 1982, Jacko et al., 1977 and CARB, 1985b). Cadmium emitted from sewage sludge incineration has been shown to occur primarily on particles less than 2 um in diameter (Bennett, et al., 1984; Radian, 1985); this is consistent with the distribution observed in other combustion emissions. The compound form emitted may be similar to those from municipal waste incineration, which is believed to be the oxide.

Resource recovery facilities are potential sources of cadmium. In municipal solid waste (MSW)-to-energy plants, cadmium present in batteries, in plastics (as stabilizers or dyes), or in other forms, will volatilize during the combustion process. The amount of cadmium emitted depends on the amount of cadmium present in the waste burned and on the efficiency of emission control equipment used to remove particulate matter from the exhaust gas. For example, the potential emission of cadmium from a planned MSW-to-energy facility (based on certain assumptions about the concentration of cadmium in the feed and the efficiency of removal), is about 5.9 kilograms (Kg) (13 pounds) per year (see Appendix C).

At this time, one MSW-to-energy facility is operating in California. Four more have received the approval of regulatory agencies. More than thirty resource recovery facilities are proposed for construction in California.

Cadmium emitted from municipal incinerators has been determined to be in the oxide form, and in the respirable size range (Radian, 1985). Measurements by Greenberg et al., (1978a, b), of cadmium on particles from municipal incinerators showed that 80 to 95 percent of cadmium is found on particles of 2 um diameter or smaller.

Cadmium emissions from fertilizer and pesticide applications are estimated to be less than 4.6 Kg (10 pounds) per year statewide.

Mobile Source Emissions

Cadmium occurs as a trace component in diesel fuel, gasoline and lubricating oil. When these fuels are burned, cadmium is emitted. Combustion of gasoline, diesel, and lubricating oil from motor vehicles is a source of 1.7 tons of cadmium emissions per year. Cadmium emitted on exhaust particulate exhibits surface enrichment (Keyser, et al., 1978).

Because cadmium sulfide is used as a curing agent in tires, particulate matter resulting from tire wear contains cadmium. Based on the number of vehicle miles traveled in California and estimates of cadmium emitted in tire particulate, tire wear is a source of 0.9 ton/year of cadmium emissions (see Appendix C for details).

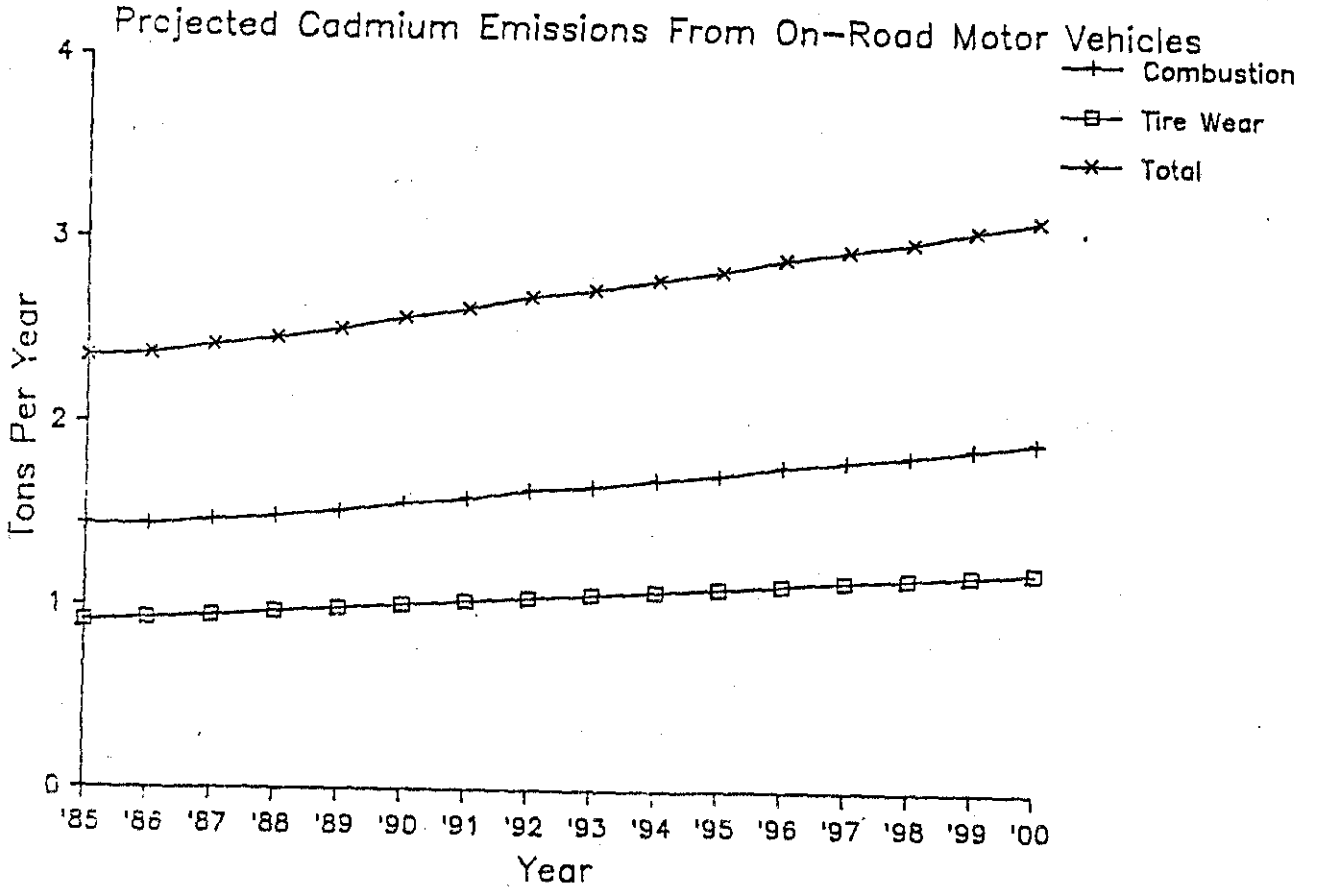
Cadmium emitted from attrition of tire rubber is thought to occur as large particles which are rapidly deposited in the immediate vicinity of the roadway. This is consistent with a study by Johnston and Harrison (1984), who measured cadmium deposition rates near a major English motorway; they found the highest concentration of particulate-associated cadmium occurred 3.8 meters from the road. Deposition rates declined to background levels at a distance of 25 meters.

Cadmium emissions from on-road motor vehicles are expected to increase due to an increase in vehicle population, vehicle miles traveled, and changes in fuel consumption. Projected cadmium emissions from on-road motor vehicles from 1985 to 2000 are depicted in Figure III-3.

C. FATE OF ATMOSPHERIC CADMIUM

Consideration of the fate of atmospheric cadmium includes both atmospheric reactions of cadmium compounds emitted from sources, and mechanisms of removal of atmospheric cadmium. There has been no characterization of atmospheric reactions of cadmium; however, there is evidence of atmospheric reactions of metal oxides. It is possible that such reactions occur with cadmium oxides emitted from combustion sources. The mechanisms of removal of cadmium from the atmosphere have been studied in many areas, including an urban area in California.

Figure III-3


Projected Cadmium Emissions From On-Road Motor Vehicles
Combustion
Tire Wear
Total
Tons Per Year
0
1
2
3
4
'85
'86
'87
'88
'89
'90
'91
'92
'93
'94
'95
'96
'97
'98
'99
'00
Year

Atmospheric Reactions

Study of the plume constituents of a large coal-burning power plant by Lindberg and Harriss (1980) indicated that as the distance from the stack increased, the water solubility of cadmium increased, and that cadmium on the smallest particles (less than 0.14 um) exhibited the greatest relative increase in concentration. It was hypothesized that this increase in solubility was due mostly to vapor condensation on the fine aerosols, causing the formation of thin, highly soluble coatings. Hansen, et al., (1984) have subsequently identified possible specific reactions of metal oxides (on coal fly ash) which explain the increase in cadmium solubility with plume "aging". These reactions include the formation of phosphates, fluorides, and sulfates:

$$6\ MO_{(s)} + P_4O_{10(g)} \rightarrow 2M_3\ (PO_4)_{2(s)} \qquad (1)$$

$$MO_{(s)} + SO_{3(g)} \rightarrow MSO_{4(s)} \qquad (2)$$

$$MO_{(s)} + 2HF_{(g)} \rightarrow MF_{2(s)} + H_2O_{(g)} \qquad (3)$$

Another reaction of metal oxides on coal fly ash has been identified (Bauer and Natusch, 1981). It was observed that metal oxides in coal fly ash could react with CO_2 to form metal carbonates. The rapid chemisorbtion of CO_2 was judged favorable for some metal oxides. If such a reaction occurs for emitted cadmium oxide, the solubility of the cadmium aerosol will remain unchanged, since both the oxide and carbonate salts are insoluble in water.

Removal of Cadmium

Cadmium is removed from the atmosphere through physical processes; both wet and dry deposition have been judged to be significant. Lindberg, et al., (1982) identified a wide range of trace metal deposition mechanisms and rates,

depending on the meteorology, canopy characteristics, or differences in local or regional emissions.

Davidson (1980) found that the rough surface dry deposition velocities of cadmium varied over a 20-fold range. For a site in Pasadena, estimates of the deposition flux of cadmium ranged from 0.30 to 0.67 ng/cm^2 day, depending on the deposition model used. Struempler (1975) measured the deposition of cadmium in precipitation to be 0.033 ng/cm^2/day at a rural site in Nebraska. Based on the residence time of aerosols, cadmium is expected to have a residence time of seven days in the atmosphere (U.S. EPA, 1980).

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IV. PUBLIC EXPOSURE

A. Atmospheric Concentrations

During 1985, ARB staff collected total suspended particulate matter (TSP) at 21 air monitoring stations in California to be analyzed for trace metals. High-volume samplers were used to collect 24-hour samples of atmospheric particulate matter of 50 um and smaller diameter (50 percent size cutoff). Monitoring sites met criteria for population oriented exposure for the criteria pollutants; all sites are in populated urban areas. Samples were collected at most sites every eight days.

Analysis was performed for each filter individually; flame atomic absorption spectrophotometry was used to determine acid-extractable cadmium. The method is described in Appendix D. A detection limit of cadmium in air of 1.0 ng/m^3, with a precision and accuracy of $\pm$ 15 percent, has been determined for the method.

Data are available for the first six months of 1985. The range of samples at each site above the detection limit ranged from 13 to 100 percent, with an average of 50 percent above the detection limit for all data. To estimate the possible range of the average concentration at each site, two methods were used. The first, termed the zero treatment method, estimates the range by assigning maximum and minimum values to all data below the detection limit. The second method, a statistical treatment, assumes the data is lognormally distributed and uses standard statistical techniques to estimate the uncertainty of the average concentration. Although the second method is believed to give the best estimate for the average, the first method is included to show the uncertainty that arises

from having data below the detection limit. In most cases the possible range of average concentration is small.

The zero treatment method assigns two different values to the data below the LOD in order to calculate the range arithmetic averages: in the first, or minimum average estimate, zero was substituted for values reported below the detection limit. For the second, or maximum average estimate, the detection limit value (1.0 ng/m^3) was substituted for values reported below the detection limit. These "min" and "max" values therefore represent the upper and lower estimates of mean concentrations possible at each site. The average concentrations derived using this zero treatment method are shown in Table IV-1.

Data from the ARB's monitoring stations were used to estimate residential population exposure to ambient cadmium in the South Coast Air Basin, the San Francisco Bay Area Air Basin, the San Joaquin Valley Air Basin, San Diego Air Basin, South Central Coast Air Basin, and Sacramento County. Exposures over the San Francisco Bay Area and the South Coast air basins were estimated by interpolating station values to census tract centroids. Exposures for the remaining air basins were estimated by assuming the entire population in each area is exposed to the arithmetic mean concentration from all sampling sites in the air basin. Table IV-2 shows the average cadmium concentrations for each air basin. For the South Coast and the San Francisco Bay Area air basins, these are population weighted averages based on the concentrations interpolated to each census tract. Average cadmium concentrations range from less than 1 ng/m^3 for Sacramento County to 2.5 ng/m^3 for the San Francisco Bay Area air basin.

The 1985 residential population in California was about 26.4 million people. The population represented in the six areas covered in our exposure

TABLE IV-1

1985 AVERAGE CADMIUM CONCENTRATIONS
ARB CADMIUM SAMPLING NETWORK
BASED ON DIFFERENT ZERO VALUE TREATMENTS*
(Six Months Data)

RANK	SITE ID	LOCATION	AVERAGES (ng/m^3) MIN	MAX	# SAMPLES ABOVE LOD	TOTAL # SAMPLES
1	0700440	Concord	5.5	5.9	22	36
2	7000579	El Monte	4.1	4.1	15	15
3	0700433	Richmond	2.9	3.0	30	32
4	9000304	San Francisco	2.5	2.6	26	31
5	2400521	Merced	1.9	2.0	13	15
6	7000087	Los Angeles	1.1	1.7	13	29
7	4300382	San Jose	1.1	1.5	18	30
8	6000336	Fremont	0.8	1.3	16	31
9	1000234	Fresno	0.7	1.1	12	22
10	8000131	El Cajon	0.8	1.0	15	21
11	4200378	Santa Barbara	0.7	1.1	11	18
12	0700430	Pittsburg	0.7	1.0	7	10
13	7000085	Pico Rivera	0.5	1.2	11	31
14	3600175	Upland	0.5	1.2	9	30
15	3900252	Stockton	0.4	1.1	8	24
16	5000558	Modesto	0.4	1.0	12	29
17	5600413	Simi Valley	0.3	1.0	6	19
18	7000072	No. Long Beach	0.3	1.0	8	31
19	1500203	Bakersfield	0.3	1.0	6	27
20	3400293	Citrus Heights	0.3	1.0	7	24
21	3300144	Rubidoux	0.2	1.0	4	31
		STATEWIDE	1.2	1.7	269	536

*Zero value treatment assigns all observations which are below the LOD a value of 0 ng/m^3 in calculating the "MIN" average and 1 ng/m^3 in calculating the "MAX" average.

TABLE IV-2

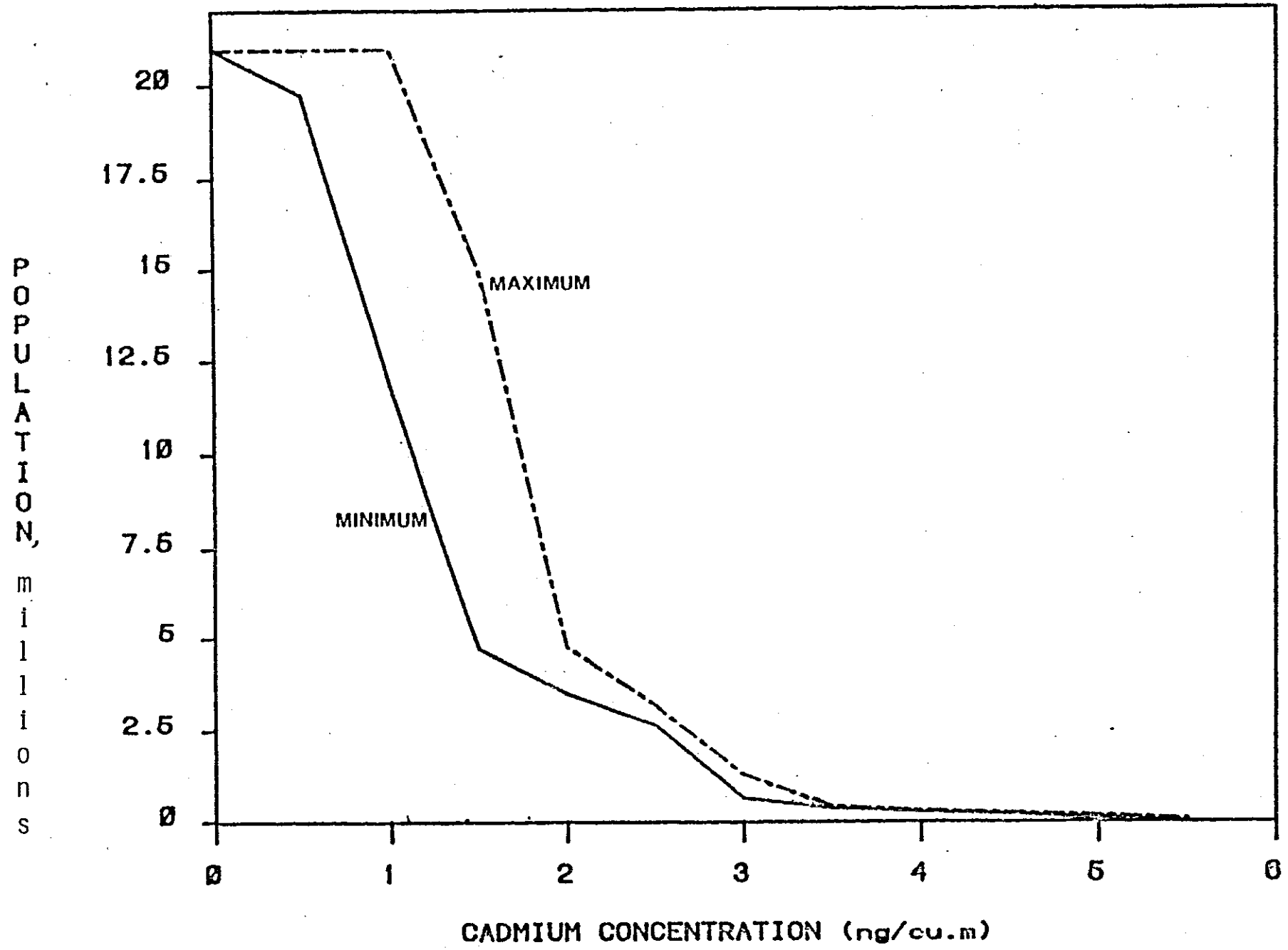
1985 AVERAGE AMBIENT CADMIUM EXPOSURE ESTIMATES
BASED ON ZERO VALUE TREATMENTS
(Six Months Data)

AIR BASIN/COUNTY	1985 AVERAGE CADMIUM EXPOSURE (ng/m^3) MINIMUM	MAXIMUM	POPULATION (millions)
San Francisco Bay Area	2.3	2.5	4.4
South Coast	1.3	1.8	10.1
San Joaquin Valley	0.7	1.3	2.3
San Diego	0.8	1.0	2.1
South Central Coast	0.5	1.0	1.1
Sacramento County	0.3	1.0	0.9
TOTALS	1.3	1.8	20.9

analysis is about 21.0 million people. No cadmium exposure estimates have been made for the remaining 5.4 million people. The following discussion of population exposure is based on an exposed population of 21 million people. Figure IV-1 shows estimated cumulative population exposure for this population using both zero value treatments. The results of this method indicate that approxmately 10 million people are exposed to annual average concentrations of cadmium of at least 1.3 ng/m^3 for the minimum average estimate and 1.8 ng/m^3 for the maximum average estimate. Approximately one million people are exposed to annual average concentrations of cadmium of at least 3.4 ng/m^3 for the minimum average estimate and 3.6 ng/m^3 for the maximum average estimate.

The range of cadmium exposure by using the two zero treatments does not include uncertainty arising from the small sample size or from large variance in measurements. To better estimate the probable range of the average atmospheric cadmium concentration, we have developed a statistical treatment for calculating 95% confidence intervals for the mean concentration at each

ESTIMATED CUMULATIVE POPULATION EXPOSURE TO CADMIUM



station. This treatment is believed to provide a better estimate of the true uncertainty associated with the calculated mean because it includes factors such as sample size, standard deviations of the data, and an estimate of the uncertainty of the sample collection and analysis procedures. A description of the statistcal treatment follows. A scatter plot of the cadmium data indicated that the data is probably distributed lognormally. Since this is commonly the case for atmospheric pollutants, it was assumed that the real distribution of ambient cadmium concentrations is lognormal. Because available software only analyzes data that is normally distributed, the cadmium data was first converted from a lognormal distribution to a normal distribution. This was done by using the logarithm of the data for the analysis. The logarithms of data that is lognormally distributed are themselves normally distributed. The statistical analysis system (SAS, 1982) software package was used for the analysis. Additionally, to complete the analysis, it was assumed that the uncertainty for sampling and analysis was 15% and that data below the LOD was equal to 1/2 of the LOD value. Setting all values below LOD to 1/2 the LOD value is expected to bias the confidence intervals to the high side of the mean.

The resulting 95% confidence interval for each station is shown in Figure IV-2. The calculated range of exposure is different from that based on the zero value treatment. For example, the 95% confidence interval calculated using the statistical treatment for the Concord site is 2.96 to 10.81 ng/m^3. This compares to a range of 5.5 to 5.9 ng/m^3 calculated using the previously discussed zero value treatment. We believe the confidence intervals from the second method provide a more realistic estimate of the uncertainty in the actual average. The estimated 95% confidence intervals for each station are shown in Table IV-3. Comparisons of the estimated

Figure IV-2

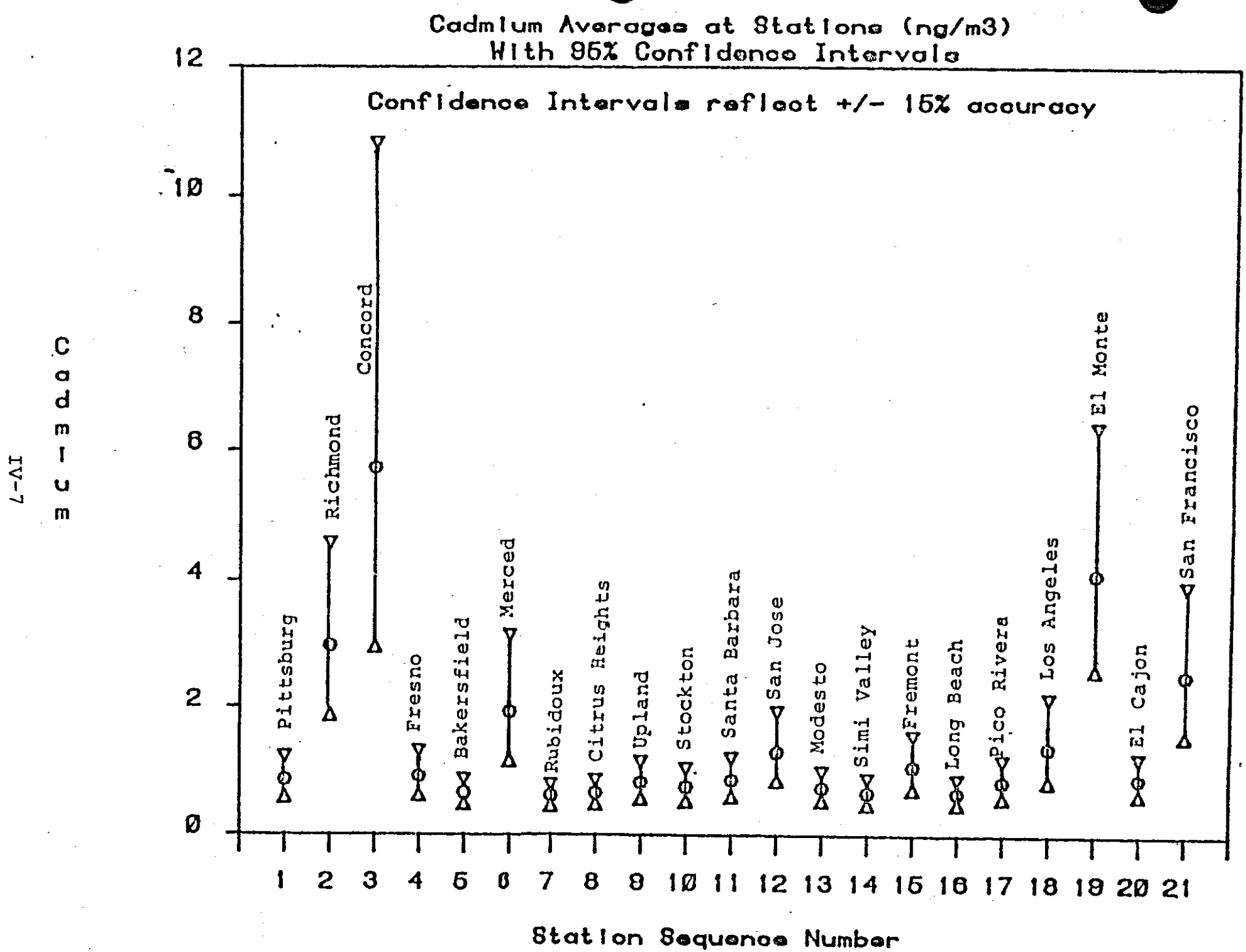

Cadmium Averages at Stations (ng/m3)
With 95% Confidence Intervals
Confidence Intervals reflect +/- 15% accuracy
12
10
8
6
4
2
0
Pittsburg
Richmond
Concord
Fresno
Bakersfield
Merced
Rubidoux
Citrus Heights
Upland
Stockton
Santa Barbara
San Jose
Modesto
Simi Valley
Fremont
Long Beach
Pico Rivera
Los Angeles
El Monte
El Cajon
San Francisco
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Station Sequence Number

TABLE IV-3

1985 AVERAGE CADMIUM CONCENTRATIONS

ARB CADMIUM SAMPLING NETWORK

WITH 95% CONFIDENCE INTERVALS

(Six Months Data)

RANK	SITE ID	LOCATION	AVERAGES (ng/m^3) MIN	MID	MAX	# SAMPLES ABOVE LOD	TOTAL # SAMPLES
1	0700440	Concord	3.0	5.7	10.8	22	36
2	7000579	El Monte	2.6	4.1	6.4	15	15
3	0700433	Richmond	1.9	3.0	4.6	30	32
4	9000304	San Francisco	1.6	2.5	4.0	26	31
5	2400521	Merced	1.2	1.9	3.1	13	15
6	7000087	Los Angeles	0.9	1.4	2.2	13	29
7	4300382	San Jose	0.9	1.3	1.9	18	30
8	6000336	Fremont	0.7	1.1	1.6	16	31
9	1000234	Fresno	0.6	0.9	1.3	12	22
10	8000131	El Cajon	0.6	0.9	1.2	15	21
11	4200378	Santa Barbara	0.6	0.9	1.2	11	18
12	0700430	Pittsburg	0.6	0.8	1.2	7	10
13	7000085	Pico Rivera	0.6	0.8	1.2	11	31
14	3600175	Upland	0.6	0.8	1.1	9	30
15	3900252	Stockton	0.5	0.8	1.0	8	24
16	5000558	Modesto	0.5	0.7	1.0	12	29
17	5600413	Simi Valley	0.5	0.7	0.9	6	19
18	7000072	No. Long Beach	0.5	0.7	0.9	8	31
19	1500203	Bakersfield	0.5	0.6	0.9	6	27
20	3400293	Citrus Heights	0.5	0.6	0.9	7	24
21	3300144	Rubidoux	0.4	0.6	0.8	4	31
		STATEWIDE	0.9	1.5	2.3	269	536

ranges in annual average concentrations on a site by site basis (Tables IV-1 and IV-3) show that the zero value treatments become unimportant when confidence intervals are used to estimate uncertainty in annual averages. The use of the zero value treatment usually results in a smaller range of uncertainty when compared to the confidence interval method except when averages are near the LOD. When averages are near the LOD both methods give comparable ranges.

Population exposures were also interpolated for the upper and lower confidence intervals for the South Coast and San Francisco air basins. The resulting average exposures for each air basin are shown in Table IV-4. The range in exposure is greater than shown in Table IV-2, while the mean is the same. The annual average cadmium concentration (weighted by population) for the San Francisco Bay Area Air Basin is now estimated to range from 1.5 to 4.7 ng/m^3 while Table IV-2 (reflecting differences due to zero value treatments) shows a range of 2.3 to 2.5 ng/m^3. On a statewide basis, we now estimate that 50% of the population is exposed to at least 1.5 ng/m^3 cadmium, as before, but the range increases from 1.3 - 1.8 ng/m^3 to 1.0 - 2.5 ng/m^3. Five percent of the population is exposed to at least 3.5 ng/m^3 with the range being expanded from 3.4 - 3.6 ng/m^3 to 1.8 - 5.6 ng/m^3. Figure IV-3 shows cadmium concentrations plotted against cumulative population for the mean and the lower and upper 95% confidence limits.

Data are available for only six months (Jan - June) of 1985. To investigate whether concentration averages calculated from this data are representative of annual average concentrations averages, data from other sources were used to compare seasonal averages with annual averages.

FIGURE IV-3

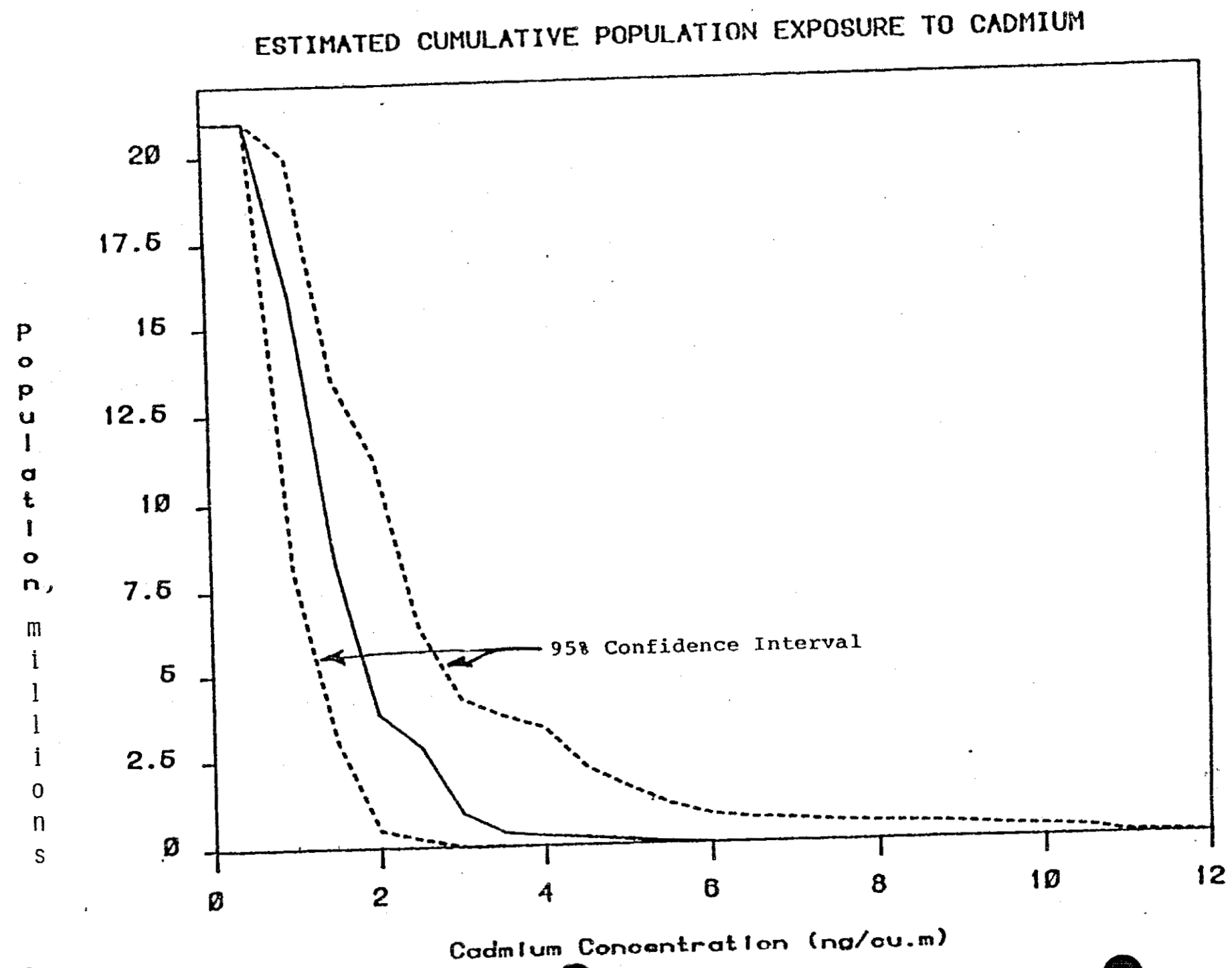

ESTIMATED CUMULATIVE POPULATION EXPOSURE TO CADMIUM
Population, millions
20
17.5
15
12.5
10
7.5
5
2.5
0
95% Confidence Interval
0
2
4
6
8
10
12
Cadmium Concentration (ng/cu.m)

TABLE IV-4

1985 ANNUAL AMBIENT CADMIUM EXPOSURE ESTIMATES
WITH 95% CONFIDENCE INTERVALS
(Six Months Data)

AIR BASIN/COUNTY	1985 AVERAGE CADMIUM EXPOSURE (ng/m^3) LOW	MEAN	HIGH	POPULATION (millions)
San Francisco Bay Area	1.5	2.4	4.7	4.4
South Coast	1.0	1.5	2.3	10.
San Joaquin Valley	0.7	1.0	1.5	2.3
San Diego	0.6	0.9	1.2	2.1
South Central Coast	0.5	0.8	1.0	1.1
Sacramento County	0.5	0.6	0.9	0.9
TOTALS	1.0	1.5	2.5	20.9

Data collected by EPA in 1977 in California show that the ratio of the first half (Jan-June) to second half (July-Dec) of the year for cadmium concentration averages varied from site to site (Table IV-5). The ratios ranged from 0.4 to 2.4 with the overall ratio being 1 for all sites. We are uncertain whether the differences in ratios between sites represent real differences in the ambient concentration or a consequence of the small sample size. When the data is examined for regional trends, the ratios for the San Francisco Bay Area range from 0.6 to 2.4 and there is a range of 0.4 to 1.9 for the Los Angeles Area. The seasonal variation of atmospheric cadmium at an urban and at a rural site in England showed that winter (Oct-March) means were higher than summer (April-Sept) means. (Harrison and Williams, 1982). This may be due to increased emissions of cadmium from increased fossil fuel

TABLE IV-5

AVERAGE CADMIUM CONCENTRATIONS DURING 1977 - FROM EPA DATABASE

LOCATION	FIRST HALF CADMIUM (ng/m^3)	FIRST HALF TOTAL # SAMPLES	SECOND HALF CADMIUM (ng/m^3)	SECOND HALF TOTAL # SAMPLES	RATIO
Anaheim	0.7	15	1.3	15	1.9
Berkeley	1.0	15	0.8	15	0.8
Burbank	2.7	15	2.5	15	0.9
Fresno	1.2	15	1.0	15	0.8
Los Angeles	2.6	15	2.6	15	1.0
Long Beach	1.0	13	1.2	14	1.2
Oakland	1.8	15	1.1	14	0.6
Ontario	2.4	15	2.2	15	0.9
Pasadena	1.3	14	1.0	15	0.8
Sacramento	0.6	15	0.7	15	1.2
San Bernadino	1.7	14	1.8	15	1.1
San Diego	1.1	15	0.9	15	0.8
San Francisco	0.7	15	1.7	15	1.0
San Jose	0.7	15	1.7	15	2.4
Santa Ana	0.7	15	0.8	14	1.1
Torrance	3.8	14	1.7	15	0.4
				OVERALL AVERAGE	1.0

combustion during the colder winter months. The January through June period for which we have 1985 data includes both 'winter' months and 'summer' months. Because the overall ratio for the first-to-second half mean concentrations was 1.0, the sampling period includes both summer and winter months, and ARB sites cover the same areas as the EPA sites, we believe that the average concentrations calculated from the available data provide a reasonable estimate of annual average concentrations for all of the California sites. However, the annual average concentration at individual sites could be different from the ARB average by a factor of 2; site-specific ratios are between one-half and two.

Further evidence to support this conclusion is that the estimates of average cadmium concentration presented in this report are in the range of concentrations measured by others in California. Saltzman, et. al., (1985) calculated a annual geometric mean cadmium concentration for the Los Angeles area of 2 ng/m^3. Sampling was carried out at eight sites during 1968-1969; 1,841 samples were collected. The authors reported that only a small fraction of samples were below the detection limit, in which case a value of one-half the detection limit was substituted. Also, data on atmospheric cadmium in California were gathered by the U.S. EPA during 1977. The U.S. EPA data contained a greater percentage than current ARB data of values below the detection limit, which limited its usefulness in estimating population exposure.

The size distribution of cadmium and its compounds were not determined in the ARB's measurements. Work by others on the size distribution of cadmium have shown that cadmium exhibits a tendency to be present at higher concentrations on small particles and to be distributed bi-modally, with a

concentration maximum in the 1 um range, and a smaller mode in the 3-10 um range. Harrison, et. al. (1971) showed this for urban aerosols in Michigan. Lee, et. al., (1968) estimated the mass median diameter of cadmium at an urban and a rural site to be 3.1 um and 10 um respectively. However, the sampling procedure employed by Lee, et. al., has been shown to bias the data to larger particle sizes, due to large particle bounce off in the first impactor stages (Dzubay, et. al., 1976; Lawson, 1980). Work on cadmium size distribution in remote areas (Davidson, et. al., 1985) yielded estimates of mass median diameters (MMD) of 0.28 and 0.56 um. Measurements in Europe of cadmium particle size (away from known cadmium sources) gave an estimate of 0.4 um MMD, and a fraction of 64 percent below 1.1 um (Duc and Favez, 1981). The MMD of atmospheric cadmium in Glasgow was determined to be 0.6 um (McDonald and Duncan, 1979). Davidson, et. al., (1981) reported a cadmium MMD of 1.5 um in an industrial section of Pittsburg, with a bimodal distribution observed. Milford and Davidson (1985) have surveyed work done on atmospheric cadmium particle size and calculated the MMD for atmospheric cadmium using data from 14 studies of remote, urban, and industrial sites. This average MMD was 0.84 um. Data from an urban California site was included in that survey; the California data (Davidson, 1977) were consistent with data from other locations. Because of the nature of cadmium sources in the State (principally high-temperature sources emitting cadmium on particles in the micron to submicron range), and the surprisingly consistent size distribution of cadmium in different studies, we believe that atmospheric cadmium in California occurs largely on particles in the respirable size range (less than 2.5 um diameter).

The compound forms of cadmium present in the atmosphere have not been determined. Study of the solubility of cadmium on particulate matter both in California (Hodge, et. al., 1978), and elsewhere (Lindberg and Harriss, 1983), indicate that 70 - 84 percent of atmospheric cadmium that is acid soluble is also water soluble. Based on the expected forms of metals emitted from combustion processes and other high-temperature processes (see Section III B, C), we conclude that atmospheric cadmium occurs primarily as the soluble sulfate, phosphate, and fluoride, with the balance occuring as the insoluble oxide or carbonate.

Because cadmium is an element found in most crustal materials at concentrations typically between 0.1-0.2 parts per million, we evaluated the contribution of crustal materials to concentrations of atmospheric cadmium. Comparison of the composition of atmospheric particulate matter to that of crustal materials has been made to assess the contribution of crustal materials to the atmospheric burden of trace metals, including cadmium. The degree of enrichment of an element in atmospheric particulate matter had been calculated as the enrichment factor, EF:

$$\frac{C_{Cd}/C_{Al}}{C_{Cd,crust}/C_{Al,crust}}$$

where C_{Cd} and C_{Al} are the atmospheric concentrations of these metals, and $C_{Cd,\ crust}$ and $C_{Al,\ crust}$ are the concentrations in the earth's crust. In most cases, average values of crustal abundance are used; in some cases, values specific to the region under study are employed. Values of EF less than 5 are considered indicative of a crustal or soil source of the element;

higher values suggest non-soil sources, including high temperature industrial processes and fuel combustion. Certain natural processes may also lead to atmospheric enrichment of certain elements: volcanism, direct sublimation from crustal materials, emissions from vegetation, and sea spray enrichment (Duce, et. al., 1975). In most urban areas, however, large EF factors are considered to be indicative of anthropogenic sources (Heindryckx, 1976). Large cadmium enrichment factors have been determined in remote areas (EF 2500) with increasing value of EF with decreasing particle size (Davidson, et. al., 1985). Lindberg and Harriss reported lower EFs for cadmium (7-23) in continental aerosols; the tendency to increasing EF with decreasing particle size was observed. Davidson et. al., (1981) found an average cadmium EF in Pittsburg of 630, and observed the same trend in increasing EF, with decreasing particle size. McDonald and Duncan (1979) reported EFs for cadmium in Glasgow ranging between 750 and 8,400, with particles in the range of 0.43 - 0.7 um exhibiting the highest EF.

Milford and Davidson (1985) provided summary statistics including cadmium EF from 14 studies in urban, rural, and industrial sites; an average EF of 1,900 was reported. This average included results of one study done in California urban area (Davidson, 1977). Based on this information, we believe it is reasonable to assume that atmospheric cadmium in California results predominantly from non-crustal sources.

Because a large amount of data on total suspended particulate matter (TSP), collected by both ARB and EPA, is available, an effort was made to determine a relationship between TSP and cadmium measurements. First, EPA cadmium data from samples collected throughout California during 1977 through 1983 were analyzed to determine if cadmium concentrations were correlated to

simultaneous occurences of total suspended particulate matter (TSP). If the two were highly correlated, cadmium concentrations could be estimated using the much larger TSP database. No significant correlations were found using the EPA data. Correlation coefficients (r) were below 0.53 at nineteen of twenty sampling sites having both cadmium and TSP data; an r value of 0.69 was calculated for cadmium-TSP data collected at Long Beach. The overall correlation coefficient was less than 0.01 for 1409 paired observations.

The same statistical calculations were made using the 1985 ARB cadmium data. To do this, we extracted twenty-four hour average TSP concentrations from the ARB air quality database for the same time periods and stations as the cadmium data contained in the ARB toxics air quality database. The cadmium-TSP correlation results for each station are given in Table IV-6. As with the EPA data, the ARB data showed little correlation between ambient cadmium and TSP concentrations, except for a few stations. Fresno data showed a very high correlation coefficient, 0.94, for a sample size of 22. The next highest correlation coefficient was 0.68 at the Upland station for 30 samples. The r value calculated for the North Long Beach site, 0.67, was quite similar to the r value calculated for the EPA Long Beach data (0.69). Thirteen of the seventeen ARB stations having comparable cadmium and TSP data had correlation coefficients below 0.54; scatter plots for the remaining three stations showed almost no variation in cadmium concentrations. As a result, we again find no useful correlations between cadmium and TSP.

All of the above discussion concerns outdoor concentrations of cadmium. ARB has made no measurement of indoor concentrations. However, Seifert, et. al., (1984) studied indoor heavy metal exposure near a secondary lead smelter,

TABLE IV-6

1985 CADMIUM AND TSP CORRELATIONS
ARB CADMIUM SAMPLING NETWORK

STATION ID	LOCATION	CORRELATION COEFFICIENT	# SAMPLES ABOVE LOD	TOTAL # SAMPLES
0700430	Pittsburg	-	7	10
0700433	Richmond	0.07	30	32
07004400	Concord	0.22	22	36
1000234	Fresno	0.94	12	22
1500203	Bakersfield	- 0.16	6	27
2400521	Merced	- 0.11	13	15
3300144	Rubidoux	- 0.06	4	31
3400293	Citrus Heights	-	7	24
3600175	Upland	0.68	9	30
3900252	Stockton	- 0.57	8	24
4200378	Santa Barbara	- 0.02	11	18
4300382	San Jose	0.53	18	30
5000558	Modesto	0.16	12	29
5600413	Simi Valley	-	6	19
6000336	Fremont	0.23	16	31
7000072	N. Long Beach	0.67	8	31
7000085	Pico Rivera	- 0.26	11	31
7000087	Los Angeles	0.47	13	29
7000579	El Monte	-	15	15
8000131	El Cajon	0.19	15	21
9000304	San Francisco	- 0.41	26	31
	STATEWIDE	- 0.09	269	536

and found that the indoor metal burden could be very different in adjacent houses. The "maintenance conditions" (window tightness) of the building (i.e., air exchange rate), and the nature of the building's immediate surroundings (vegetation), which would effect deposition and reentrainment, were believed to be significant factors in influencing indoor metal concentrations. Because of the lack of available data relating indoor to outdoor cadmium concentrations, no attempt was made to estimate indoor cadmium exposure.

C. Exposure Close to Sources

To evaluate increased exposure to atmospheric cadmium for people living close to sources, we calculated the cumulative air quality impact of three secondary copper smelters in the South Coast Air Basin. Emissions from the three facilities were estimated by making certain assumptions using information on the process rate (tons of scrap processed per year), facility operations, and an emission factor of 3.0 lb cadmium/ton of scrap. This emission factor was derived from information on the cadmium content of various types of copper scrap. Cadmium emissions from three smelters were estimated to range from 1.7 to 3.4 tons/year. The upper value represents maximum worst case emissions, and the lower value represents a worst-plausible case.

The range of emissions rate estimates for each of the three smelters was used as input to the Gaussian air quality model Industrial Source Complex - short term (ISCST). Historical meteorological data from a station close to the sources for three years (1976, 1977, and 1978) were used to run the model. The difference in meterological conditions among the three years yield variations in results which were small. Results produced using 1977 mèt data (the highest results) are discussed here. Where stack parameters for the sources were available, they were used; in some cases, the data were unavailable and the stack parameters which would yield worst case ambient concentrations were used. Because of the assumptions made, we do not expect cadmium exposure due to emissions from these sources to be higher than our estimates. To estimate exposure, the modeled ambient concentrations were superimposed on the population data for the area based on census tract centroids. The area contained a residential population of 5.7 million.

Figure IV-4 shows the cumulative exposure attributable to emissions from these three smelters.

The modeled exposure levels were: 20 ng/m^3 for 57,000 people; 5-7 ng/m^3 for 290,000 people; and 0.5 - 0.6 ng/m^3 for 2.8 million people. The exposure estimates, based on maximum possible emission rates, are double these values. The general exposure in the South Coast Air Basin (based on direct measurement of atmospheric cadmium) has been estimated to be 1-2.3 ng/m^3.

In interpreting data on exposure close to sources of cadmium, it should be realized that sources of cadmium emissions usually are also emitters of other metals and compounds which may have potential adverse health effects. It is beyond the scope of this report to quantitatively address this issue; Table IV-7 lists non-criteria pollutants which may have chronic health effects which are known or are likely to be emitted from cadmium emission sources.

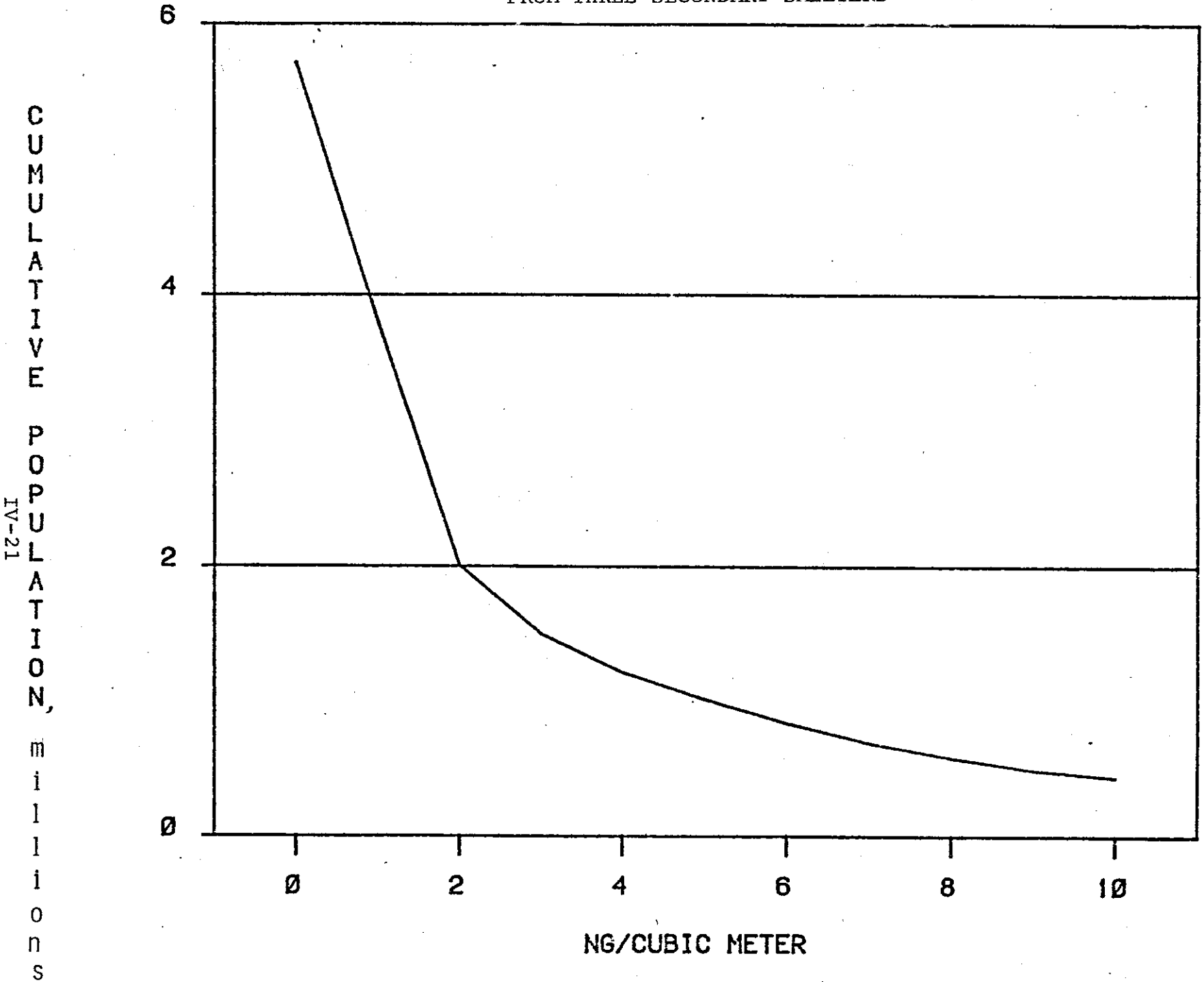
Table IV-7

Selected Non-Criteria Pollutants Which May be Emitted from Sources of Cadmium

Source Type	Pollutants
Combustion processes	Metals (arsenic, mercury, nickel); polycyclic aromatic hydrocarbons (PAH); chlorinated dioxins
Smelters	Lead; arsenic; chromium; chlorinated dioxins
Gasoline-powered vehicles	Benzene, ethylene dibromide; ethylene dichloride; PAH

Fig. IV-4

ESTIMATED CADMIUM EXPOSURE DUE TO EMISSIONS
FROM THREE SECONDARY SMELTERS



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APPENDIX A

INFORMATION REQUEST LETTER WITH ATTACHMENTS AND RESPONSES

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

February 4, 1985

Dear Sir or Madam:

Subject: Request for Information Regarding Cadmium

I am writing to request information on the health effects of cadmium as part of our toxic air contaminant program. This program is based on Health and Safety Code Sections 39650, et seq. which require the ARB to identify compounds as toxic air contaminants and once identified to develop and adopt control measures for such compounds. After consultation with the staff of the Department of Health Services (DHS), we have selected cadmium as a candidate toxic air contaminant to be evaluated in accordance with the provisions of Health and Safety Code Sections 39650, et seq. During our evaluation of cadmium, we will consider available health information on all forms and compounds of cadmium. Additionally, we are soliciting information regarding environmental and biological transformations of cadmium and its compounds.

Before the ARB can formally identify a compound as a toxic air contaminant, several steps must be taken. First, the ARB must request the Department of Health Services to evaluate the health effects of candidate compounds. Second, the ARB staff must prepare a report which includes the health effects evaluation and then submit the report to a Scientific Review Panel for its review. The report submitted to the Panel will be made available to the public. Information submitted in response to this request will be considered in the ARB report to the Panel. Although any person may also submit information directly to the Panel for its consideration, I urge you to submit all information at this time for our consideration in the development of the report for the Panel. The Panel reviews the sufficiency of the information, methods, and data used by the DHS in its evaluation. Lastly, after review by the Scientific Review Panel, the report with the written findings of the Panel will be considered by the Air Resources Board and will be the basis for any regulatory action by the Board to officially identify a compound as a toxic air contaminant.

Prior to formally requesting the DHS to prepare a health effects evaluation of cadmium, we are providing, pursuant to the provisions of Section 39660(e) of the Health and Safety Code, an opportunity to interested parties to submit information on the health effects of cadmium which he or she believes would be important in DHS's evaluation of cadmium as a candidate toxic air contaminant.

In January 1985, ARB staff received a reference search on cadmium health effects using the MEDLINE and TOXLINE Information Services. These information services include material available to the public on or before September 1984. The attached bibliography lists the references from this information search. We are requesting pertinent information on cadmium health effects, including any material that may not be available to the public, that is not included in the attached bibliography.

Pursuant to the provisions of the Public Records Act (Government Code Sections 6280 et seq.), the information you provide will be a public record and subject to public disclosure, except for trade secrets which are not emission data or other information which is exempt from disclosure or the disclosure of which is prohibited by law. The information may also be released to the Environmental Protection Agency, which protects trade secrets and confidential information in accordance with federal law, and to other public agencies, which are also required to protect such information.

To expedite the review process, we ask that any information which you believe should be regarded as "trade secret" be clearly marked and separated from other information. You may identify portions of the information you submit as "trade secret" in accordance with Health and Safety Code Section 39660(e). The claim of trade secrecy must be supported upon the request of the Air Resources Board. Other information claimed to be trade secret and information otherwise claimed to be exempt from disclosure may be identified as confidential in accordance with Section 91011, Title 17, California Administrative Code. Section 91011 requires that the claim of confidentiality be accompanied by specified supporting information.

I would appreciate receiving any relevant information you wish to submit by March 22, 1985. Your help in expediting our review will be greatly appreciated. Please send the information to the attention of:

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Cadmium
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

If you have any further questions regarding health effects information, please contact Mr. John Batchelder at (916) 323-1505. For any other questions, please contact Mr. Robert Barham at (916) 322-7072.

If you are not the person to whom this request should be addressed, please forward it to the appropriate person in your organization. Also, please let us know whether you would like to continue to receive information inquiries for other candidate compounds, and if not, if there is anyone in your organization to whom such requests should be sent.

Sincerely,

Peter D. Venturini, Chief
Stationary Source Division

cc: Alex Kelter, DHS
Lori Johnston, DFA
Wayne Morgan, President, CAPCOA
Jan Bush, Executive Secretary, CAPCOA
David Howekamp, EPA Region IX
Assemblywoman Sally Tanner, Chairwoman, Committee on Toxic Materials
Senator Ralph Dills, Chairman, Committee on Governmental Organization
Senator Art Torres, Chairman, Committee on Toxics and Public Safety Management
Emil Mrak, Chairman and Scientific Review Panel Members
APCOs

Attachment

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TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CADMIUM

PART B:

HEALTH EFFECTS OF CADMIUM

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EXECUTIVE SUMMARY

Executive Summary

Cadmium is a silvery-white metal found primarily in the +2 oxidation state. Although cadmium is not known to be an essential element, it is chemically similar to zinc and other biologically essential elements. This similarity is an important factor in cadmium-induced toxicity since cadmium may replace these essential elements biochemically and interfere with important physiological processes.

For the general population, the major sources of exposure to cadmium are through food and smoking. For occupationally exposed populations, inhalation may be the major route of exposure. Ambient airborne cadmium may also become a significant exposure route in industrial areas.

Although ingestion is the major route of exposure, only one to ten percent of ingested cadmium appears to be absorbed systemically. Pulmonary absorption of inhaled cadmium is estimated to range from 10 to 50 percent of deposited cadmium. Animal studies indicate that some soluble and insoluble cadmium salts are handled in a similar manner in the respiratory tract. Together the liver and kidney account for about 50 percent of the cadmium body burden, with 30 percent found in the kidneys. The biological half-life of cadmium in humans has been estimated to range from 10 to 30 years.

Cadmium has moderate acute toxicity, producing gastrointestinal or pulmonary effects from ingestion or inhalation, respectively. Subchronic and chronic exposures to cadmium have been associated with a wide range of adverse outcomes that include cardiovascular, endocrine, hepatic, bone, hematological, immunological, respiratory, renal, reproductive, and teratogenic effects. The staff of the California Department of Health Services (DHS) has concluded that renal toxicity is the most sensitive noncarcinogenic effect, because it occurs at lower exposure levels than other noncarcinogenic effects.

The staff of the Air Resources Board has estimated that the ambient airborne concentration of cadmium in California is in the range of 1 to 2.5 ng/m^3. A daily retention rate of cadmium estimated to induce renal toxicity in 10 percent of the population has been estimated to be 6.6 to 24.6 μg/day over a 50-year period. Ambient air concentrations necessary to attain this range of retention rates have been estimated to be 650 to 2500 ng/m^3, assuming 50 percent pulmonary absorption. Although no threshold exposure level has been determined for renal toxicity, the staff of DHS believes that such a level does exist. The staff of DHS has concluded that the two to three orders of magnitude difference between the estimated ambient levels of cadmium and those concentrations necessary to attain a retention rate at which 10 percent of the population would develop renal toxicity is sufficiently large that ambient airborne cadmium does not pose a significant hazard. Since renal toxicity is the most sensitive noncarcinogenic endpoint, the staff of DHS does not expect any other acute or chronic noncarcinogenic toxic effects from current ambient levels.

In addition, cadmium has induced cancer in experimental animals and has been associated with an increase in human cancers in epidemiological studies. Cadmium has produced injection site tumors (in rats) and remote tumors (in rats and mice) following subcutaneous or intramuscular injections, and has produced lung tumors in rats exposed to cadmium chloride aerosol. Several studies in which cadmium was given by the oral route have been negative, perhaps because of poor gastrointestinal absorption and low susceptibility of gastrointestinal epithelial tissue to carcinogenesis induced by cadmium. The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of carcinogenicity in animals and that, for practical purposes, cadmium should be regarded as if it presents a carcinogenic risk to humans. DHS staff concurs in these conclusions.

Epidemiological evidence has suggested an association between cadmium exposure and neoplasia, including respiratory, renal, prostatic, and bladder cancers. For the latter three cancers the evidence is suggestive or inconclusive; however, there is strong evidence of an association between cadmium exposure and an increased risk of respiratory cancer. Several occupational studies have shown some association between cadmium exposure or potential exposure and lung cancer. A recently published, well-designed study which evaluated a cohort of cadmium-exposed workers, found a highly statistically significant dose-response relationship. Neither bias nor confounding appeared to be responsible for the observed excess lung cancer risk.

A variety of studies have indicated that cadmium is mutagenic and clastogenic. However, a number of similar studies have given negative

results. Therefore, the staff of DHS has concluded that there is only limited evidence that cadmium is mutagenic and clastogenic.

There is also evidence that cadmium can bind to DNA and cause mispairing of synthetic polynucleotides. This type of activity may also cause a mutagenic or carcinogenic effect. The mechanism of action for this type of effect is postulated to have no threshold associated with it. In the absence of compelling evidence of a threshold, the staff of DHS considers the mechanism of cadmium carcinogenesis to be a nonthreshold process.

The estimated ambient airborne concentrations of cadmium were predicted to present a potential carcinogenic risk to humans. Two separate cancer risk assessments were performed, both of which assumed that cadmium carcinogenicity operates through a nonthreshold mechanism. One was based on a mortality study of workers in a cadmium production plant. A direct linear model that incorporated an adjustment for the "healthy worker effect" was fitted to the exposure data and corresponding standardized mortality ratios for respiratory cancer. The second cancer risk assessment was based on rat lung tumor incidence in a 27-month inhalation bioassay of soluble cadmium chloride aerosol. Several models were fitted to these data, including the multistage model. Predictions of cancer risks at ambient air concentrations in California were obtained by extrapolating 3 to 4 orders of magnitude down from either the experimental rat exposures or the occupational exposures. For continuous lifetime exposure to 1 ng/m^3 cadmium, the human-based assessment predicted the range of excess lifetime cancer risks to be 2 per million (best estimate) to 12 per million (upper 95% confidence limit). The animal-based assessment predicted the range of excess lifetime cancer risks

to be 110 per million (maximum likelihood estimate) to 180 per million (upper 95% confidence limit). The upper 95% confidence limit for risk based on the animal data is about 15 times the upper 95% confidence limit predicted by the human data. The best estimate from the animal data is about ten times the upper 95% confidence limit of risk predicted by the human data. (See Table I-1 and Figure I-1.)

The DHS staff believes that a discrepancy of one to two orders of magnitude between animal- and human-based risk estimates is relatively small. Because the human data for exposure and for response were not found to have any major deficiencies, and because a conservative linear extrapolation was used, DHS staff has determined that reliance on the human-based risk assessment is unlikely to underestimate risk. The range of recommended risk estimates is therefore provided by the human-based risk assessment.

The hazard posed by atmospheric cadmium to residents of California was estimated by applying the risk estimate to cadmium concentrations measured in the state. Noncancer health effects are not expected to occur at concentrations of cadmium measured in populated areas of the state. In contrast, carcinogenic effects may occur at levels of cadmium measured in ambient air. The upper-bound excess lifetime cancer risk from estimated atmospheric concentrations of cadmium in California has been estimated to range from 2 per million to 30 per million. This is a health-conservative estimate; the actual risk may lie in or below that range.

DHS staff emphasizes that the risk estimates derived in conducting a risk assessment are not exact predictions, but rather represent best estimates

based on current scientific knowledge and methods. Uncertainty in this risk assessment stems from (1) limitations in the data on which the assessment was based, (2) an extrapolation from occupational exposure levels to current ambient cadmium concentrations ranging over three to four orders of magnitude, (3) generalization from the mortality experience of adult white males in Colorado to the general population in California, (4) differences between occupational and nonoccupational exposures in terms of particle size distribution, and (5) potential inaccuracy and variability of ambient exposure measurements.

The DHS staff has determined that the possible roles of chance, bias and/or confounding in distorting the true dose-response relationship in the occupational study were likely to have been small. The DHS staff has also concluded that inaccuracies in the evaluation of exposure and cancer mortality in that study were likely to have been small. In addition, the net direction of these potential errors was likely to result in an overestimate of cadmium's potency. For these reasons, the DHS staff believes that the use of these epidemiologic data in a quantitative risk assessment is appropriate. Furthermore, the use of human data eliminates uncertainty arising from interspecies extrapolation. Since the occupational exposures were by inhalation, there is no extrapolation between routes of exposure.

The DHS staff recommends that the range of risks for ambient exposures to cadmium be based on the best estimate and upper 95% confidence limit predicted from fitting a linear model to the human data. The range of estimated excess lifetime cancer risks from 24-hour-per-day exposure for a

lifetime to average ambient airborne concentrations, estimated to be 1 to 2.5 ng/m^3 cadmium, is 2 to 30 per million persons exposed. In "hot spots" identified in California, the range of estimated excess lifetime cancer risks from 24-hour-per-day exposure for a lifetime to an average of 40 ng/m^3 of cadmium is 80 to 480 per million persons exposed. The ARB staff has estimated that approximately 57,000 people may be exposed to the average hot spot ambient level.

Based on the finding of cadmium-induced carcinogenicity and the results of the risk assessment, DHS staff finds that ambient cadmium is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

TABLE I-1

ANIMAL AND HUMAN BASED PREDICTIONS

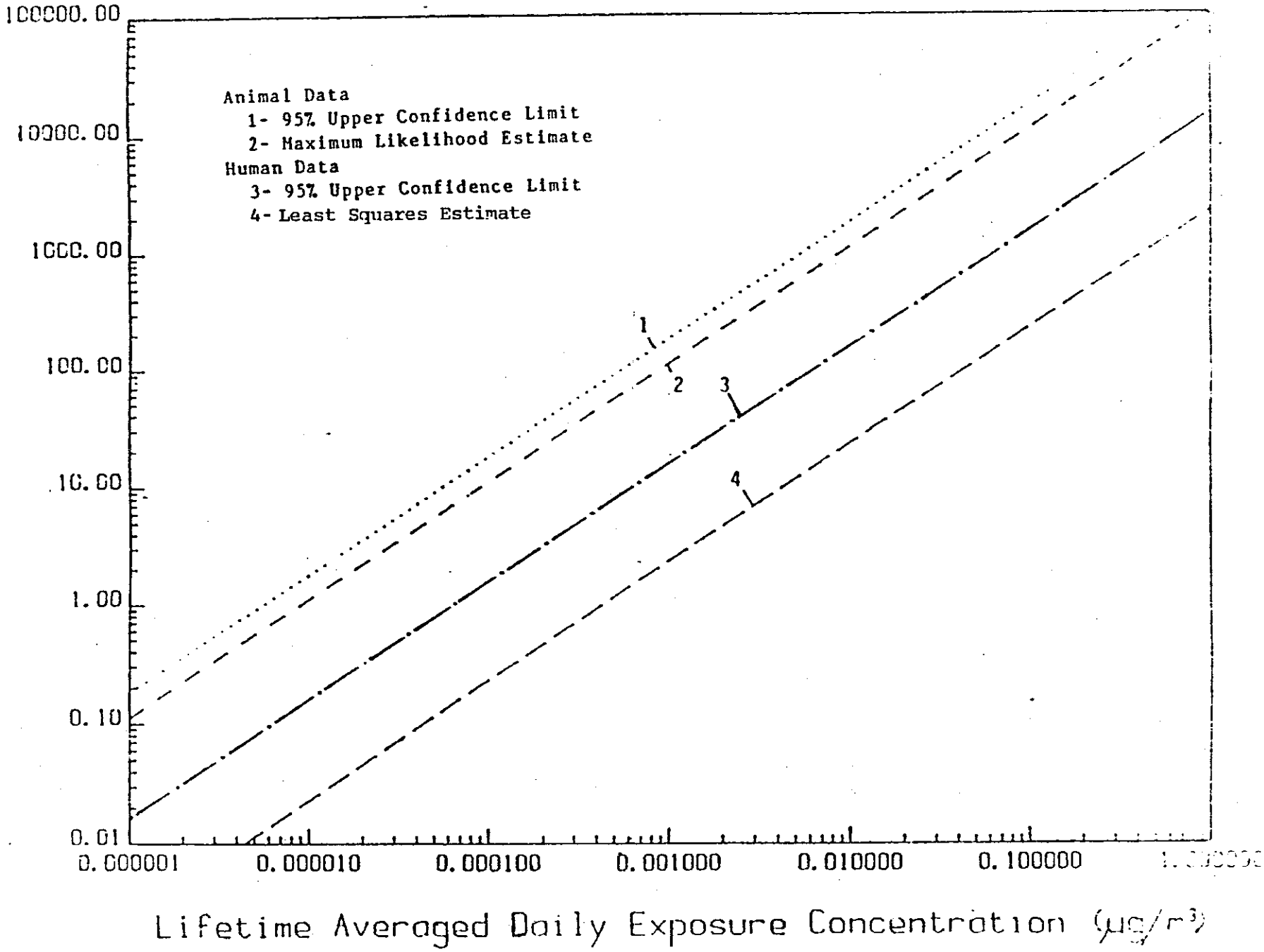
OF EXCESS LIFETIME CANCER RISKS PER MILLION PERSONS

EXPOSED TO AMBIENT AIRBORNE CONCENTRATIONS OF CADMIUM

	Ambient Air Concentration		
	1 ng/m^3	2.5 ng/m^3	40 ng/m^3
	Overall mean in California	UCL of overall California mean	hot spot mean
ANIMAL DATA			
95% Upper Confidence Limit	$180/10^6$	$450/10^6$	$7200/10^6$
Point Estimate	$110/10^6$	$275/10^6$	$4400/10^6$
HUMAN DATA			
95% Upper Confidence Limit	$12/10^6$	$30/10^6$	$480/10^6$
Point Estimate	$2/10^6$	$5/10^6$	$80/10^6$

Figure I-1

ESTIMATES OF HUMAN EXCESS LIFETIME CANCER RISK BASED ON ANIMAL AND HUMAN DATA



II. Introduction

Cadmium was first identified as a distinct element in 1817. During the 1800s there were some reported cases of cadmium poisoning from inhalation of cadmium fumes or dust; however, it was not until the second or third decade of the present century that cadmium was recognized as a significant occupational health problem. Occupational exposure has been associated with acute and chronic respiratory effects and renal toxicity. Environmental exposure to cadmium has been considered to play an etiological role in Itai-Itai disease, a disease where the patients have severe osteoporosis and osteomalacia. Many other toxic effects in humans and experimental animals have now been associated with cadmium exposure.

There has been a tremendous effort to study the adverse effects of cadmium, and a vast literature on the subject has accumulated. This literature has been reviewed and evaluated by many authors. Some of the most comprehensive reviews are by Friberg et al. (1974) and EPA (1981, 1985). These reviews are referred to extensively in the present document.

III. Properties and Uses

Cadmium is a relatively rare element that makes up about 1.5×10^{-5} percent of the earth's crust. It is a transition element in group 2b of the periodic table, which also includes zinc and mercury. This chemical similarity between cadmium and zinc is an important factor in cadmium toxicity, as will be discussed in the document. Cadmium is usually obtained as a by-product from the processing of zinc, lead, and copper ores, where it is primarily found as cadmium sulfide. The elemental form of cadmium is a soft silvery-white metal that has a molecular weight of 112.4. Its most common oxidation state is +2, although a few compounds have been reported in which cadmium is in the +1 oxidation state (Hollander and Carapella 1978). Cadmium salts, as with most metal salts, range from highly water soluble to insoluble (see Table III-1). The predominant form of cadmium found in air pollution is cadmium oxide, although other forms may be present.

Cadmium has a number of economic uses, such as in metal finishing, pigments, batteries, stabilizers in plastics, electronic application, and catalysts. The major use is in the electroplating industry, which accounts for over half of the cadmium usage in the United States (Parker 1978).

The major source of cadmium release to the environment is from solid wastes, such as coal ash, sewage sludge, flue dust, and fertilizers (Parker 1978). An increasingly greater source of cadmium release is from plastics burned in municipal waste incinerators (Yost 1979).

Table III-1

Some Physical Properties of Selected Cadmium Compounds[a]

Chemical Name	Formula	Molecular Weight	Water Solubility ($g/100gH_2O$/Temp°C)
Cadmium	Cd	112.4	Insoluble, soluble in dilute nitric or sulfuric acid
Cadmium acetate	$Cd(C_2H_3O_2)_2$	230.5	Soluble
Cadmium carbonate	$CdCO_3$	172.4	Insoluble (2.8×10^{-6}), soluble in acids
Cadmium chloride	$CdCl_2$	183.3	Soluble (128.6/30)
Cadmium fluoride	CdF_2	150.4	Soluble (4.35/25)
Cadmium nitrate	$Cd(NO_3)_2$	236.4	Soluble (109/0)
Cadmium oxide	CdO	128.4	Insoluble (9.6×10^{-4}), soluble in acids
Cadmium sulfate	$CdSO_4$	208.5	Soluble (76.6/20)
Cadmium sulfide	CdS	144.5	Insoluble (1.3×10^{-4}/18), soluble in acids

[a] Source: IARC 1976, Hollander and Carapella 1978

IV Routes of Exposure

A. Food and Smoking

The major exposures to cadmium are through food and smoking. Several food crops, including potatoes, root crops, and leafy vegetables, are known to take up and concentrate cadmium from the soil (Pahren et al. 1978). Daily intake of cadmium from food and water has been estimated to be 39 μg/day for a 15-to 20-year-old male (FDA 1974).

Smoking can contribute a significant proportion of an individual's daily exposure to cadmium. It is estimated that 0.1 to 0.2 μg of cadmium are inhaled with each cigarette (EPA 1980a). Therefore, smoking one pack per day (20 cigarettes) can increase the daily cadmium intake by about 10% (2 to 4 μg/day).

B. Occupational

Occupational exposure is primarily through inhalation of airborne cadmium. It is the greatest source of exposure for this cadmium worker population. The present OSHA standards for occupational exposure are 100 $\mu g/m^3$ for cadmium fumes and 200 $\mu g/m^3$ for cadmium dust on a time weighted average for an eight-hour workday (NIOSH 1984a). The American Conference of Governmental Industrial Hygienists (ACGIH 1984) has established the Threshold Limit Value (TLV) for an eight-hour exposure at 50 $\mu g/m^3$. NIOSH has recommended that the standard be set at 40 $\mu g/m^3$ for a time weighted average of a 10-hour workday, 40-hour workweek (NIOSH 1984a). Assuming an

average air intake of 10 m^3 during the working day, daily exposure could range from 400 to 2000 μg of cadmium if exposures occurred at levels between the NIOSH recommended level and the current OSHA standard.

C. Pollution

Environmental pollution can increase cadmium exposure via ingestion and inhalation. Cadmium soil levels in crop lands can be increased by use of phosphate fertilizers or municipal sludge, both of which contain high levels of cadmium. Deposition of airborne cadmium on crop land can also increase cadmium soil levels.

Airborne cadmium is primarily from anthropogenic sources. Highest levels are found in industrialized cities and around smelting operations. When no significant sources of cadmium pollution are present the airborne concentration is generally around 1 ng/m^3 (EPA 1980a). Assuming an average daily inhalation volume of 18 m^3, the daily exposure from ambient air would be about 20 ng.

V. Pharmacokinetics and Metabolism

Inhalation is the primary route of exposure to airborne cadmium. However, swallowing particulates initially deposited in the upper respiratory tract may also play a role in exposure to inhaled cadmium. Airborne cadmium is primarily found as the oxide, although other insoluble and soluble salts may be present. These salts can be pure or a mixture in an aerosol or in dust. The deposition of cadmium in the respiratory system is dependent on the size of inhaled particles.

The Task Group on Lung Dynamics (1966) defined the different portions of the respiratory system as: (1) the nasopharynx, which begins with the anterior nares and extends to the larynx or epiglottis, (2) the tracheal/bronchial portion, extending from the trachea to the terminal bronchioles, and (3) the pulmonary portion, which extends from the respiratory bronchioles to the alveolar sacs. Deposition in the pulmonary portion of the respiratory system is usually of greatest concern because clearance is much slower than in the other portions. Large particles (10 to 100 μm) tend to be almost completely removed in the nasopharynx. Particles of 5 to 10 μm still tend to be trapped in the nasopharynx, but 5 to 25 percent may be deposited in the pulmonary portion. About 20 to 30 percent of particles from 0.5 to 5 μm are deposited in the pulmonary portion and up to almost 70 percent of smaller particles may be deposited. Some small particles (0.1 to 0.5 μm) may be exhaled. In a person breathing at a moderate work rate (20 liters/min), about 10 to 60 percent of particles with a mass median diameter of 0.01 to 5 μm would be deposited in the pulmonary compartment (Task Group

on Lung Dynamics 1966). The model used by the Task Group assumed nasal breathing only. Deposition may be greater in the pulmonary portion when breathing occurs through the mouth. Milford and Davidson (1985) estimated the proportion of cadmium deposition in the pulmony compartment during mouth breathing. They estimated 11 to 27 percent of the airborne cadmium would be depositied using respiration rates of 7.5 to 30 liters per minute. Particle size distribution was based on measurements from a number of different studies at a variety of locations. The mass median aerodynamic diameter in this analysis was 0.84 μm.

Particles trapped in the upper respiratory tract and those deposited on tracheal and bronchial mucosa will be cleared by mucociliary activity and swallowed. Some particles deposited in the lower respiratory tract may be phagocytized by pulmonary macrophages and transported out of the lung by mucociliary activity. Thus, absorption of cadmium from the lung and gastrointestinal tract both need to be considered. In addition, the greatest source of cadmium exposure for the general population is via food, which makes the gastrointestinal tract the primary site of cadmium absorption.

A. Absorption from the Lungs

Friberg et al. (1974) reviewed several animal inhalation studies and a study comparing the body burdens of cadmium in smokers versus nonsmokers, then estimated the proportions of cadmium absorbed. From acute exposure studies on dogs (Harrison et al. 1947) and mice (Potts et al. 1950), they estimated absorption of 40 and 10 percent, respectively. A 30 percent absorption was estimated from a chronic exposure study in rabbits (Friberg 1950). The

cadmium body burden in smokers (Lewis et al. 1972) suggested that absorption was as high as 27 percent. EPA (1981) cites a reference (Task Group on Lung Dynamics 1966) that indicates absorption of cadmium from human lungs could range from less than 20 to 50 percent, depending on particle size, solubility, and other factors.

Absorption may be dependent on the solubility of the chemical form of the inhaled cadmium; however, some animal studies suggest otherwise, at least for cadmium chloride and cadmium oxide. Oberdorster et al. (1979) compared the lung clearance of cadmium chloride and cadmium oxide in rats following administration via inhalation. Since the aerosols of both compounds had similar particle size distributions and were administered at similar airborne concentrations, solubility was the major variable. The difference in solubility did not prove to have a significant effect on long-term clearance from the lung since both cadmium compounds had half-lives of 67 days. Short-term clearance was not observed for cadmium chloride, but was seen for cadmium oxide. In a later study, however, Oberdorster et al. (1980) reported short-term lung clearance of cadmium chloride. Oberdorster et al. (1979, 1980) interpreted the similar long-term clearance of the two compounds from the lung as indicating that both compounds were handled in the same manner. They suggested that in both cases cadmium protein binding may be involved and followed by absorption via alveolar clearance pathways.

Short-term clearance would probably include bronchial clearance and cadmium would end up in the gastrointestinal tract. However, Hadley et al. (1980) found that a large amount of the intratracheally instilled cadmium oxide that was removed from rat lungs during short-term clearance was found in the liver. This indicates that much of the cadmium oxide was solubilized and

absorbed systemically. Since absorption from gastrointestinal tract is limited, as will be discussed in Section V.B, much of the short-term clearance must be from pulmonary absorption.

The extent of short-term clearance for cadmium oxide that was observed by Hadley et al. (1980) was greater than that for cadmium chloride observed by Oberdörster et al. (1980) following intratracheal instillation. The reason for the difference has not been examined.

Friberg et al. (1974) has concluded from a review of the available information that animal experiments indicate 10 to 40 percent of inhaled and deposited cadmium is absorbed from the lung. Information on absorption from human lungs of cadmium in cigarette smoke indicates that it is from 25 to 50 percent. Thus, a range of 10 to 50 percent of inhaled cadmium deposited in the lung may be systemically absorbed.

B. Absorption from the Gastrointestinal Tract

Several animal studies have been performed to determine the magnitude of cadmium absorption from the gastrointestinal tract. These studies, reviewed by Friberg et al. (1974), indicate that most ingested cadmium, about 96 to more than 99%, is not absorbed and is excreted in the feces. Human studies, also reviewed by Friberg et al. (1974), indicated that absorption was from 1 to 10 percent of ingested cadmium.

Factors found to influence cadmium absorption from the gastrointestinal tract include age and nutrition. Engström and Nordberg (1979) report that one-month-old mice retained 5.2% of an orally administered dose while three-

and six-month old mice retained only 2.9 and 2.1% of administered doses, respectively. Several studies have shown that a calcium deficient diet causes an increased cadmium uptake by the gastrointestinal tract, and one study suggested that vitamin D increases cadmium uptake (Friberg et al. 1974). Low protein diets have been found to increase the amount of cadmium absorbed (Suzuki et al. 1969).

C. Distribution and Storage

Once cadmium is absorbed it enters the circulatory system. Animal studies indicate that cadmium will initially be found in the plasma. Levels in the plasma fall rapidly, but then cadmium levels in the red blood cells rise. Cadmium associated with the red blood cells is bound to proteins such as metallothionein and hemoglobin. Continuous exposure produces an increase in the concentration of cadmium in the blood, but a plateau occurs at a certain blood level. When exposure ends cadmium blood levels will decrease (Friberg et al. 1974).

Together the liver and kidney account for about 50 percent of the cadmium body burden, with 30 percent found in the kidneys. Other organs in which cadmium accumulates are the spleen, pancreas and testes (Probst 1979). Initially the concentration of cadmium increases faster in the liver than the kidney. In the liver most cadmium is bound to a low molecular weight protein, metallothionein. This protein bound cadmium is believed to be the form in which cadmium is redistributed from the liver to the kidney (Norberg 1972, Tanaka et al. 1975). Within the kidney the highest concentration of cadmium is found in the cortex. The level of cadmium in the renal cortex

increases until renal toxicity occurs, at which point urinary cadmium excretion will increase and renal cortex levels decrease. This is from a lack of uptake of cadmium-bound metallothionein by damaged renal tubular cells and the loss of cadmium in sloughed renal tubular cells.

D. Excretion

Generally, excretion of absorbed cadmium is very slow because little cadmium is lost in the urine since there is efficient uptake by the renal tubular cells. In mice, daily renal excretion accounts for about 0.01 to 0.02 percent of the total body burden. Animal studies have been been conducted to estimate the biological half-life of cadmium. It was found to vary from about 200 days in mice to 1.5 years in squirrel monkeys. The biological half-life of cadmium in humans has been estimated using mathematical models to range from 10 to 30 years (Friberg et al. 1974).

E. Metallothionein Binding

Metallothionein is a small molecular weight protein that appears to play an important role in cadmium's metabolism. Two distinct forms of this protein are usually found in tissues. They differ slightly in amino acid composition (Winge and Meklossy 1982). Metallothionein can bind cadmium, zinc, copper and mercury. The relative affinities of rat kidney metallothionein for these four metals are in the order of mercury>copper>cadmium>zinc (Foulkes 1982). This is probably the same order found for metallothionein in other tissues and species.

Metallothionein is in many tissues, with the highest concentrations found in the liver and kidney, where the highest levels of cadmium are also found. Most of the cadmium (80%) in these two organs is bound to metallothionein. In the kidney most metallothionein contains cadmium and zinc, followed by copper (Kagi et al. 1984). As the cadmium concentration in the kidney increases, there is a proportional increase in the concentration of zinc (Friberg et al. 1974). At high cadmium concentrations, the zinc concentration no longer increases.

Metallothionein synthesis is induced when cadmium or zinc is given pareterally. Induction is greatest in the liver, although it is also induced in other tissues such as the kidney and pancreas. The biological halflife of metallothionein has been found to be relatively short (5 days or less), especially when compared to the biological half-life of cadmium. Thus, cadmium and zinc ions are released by degradation of the protein and then are bound to new metallothionein that is constantly being synthesized.

The physiological role of metallothionein is not fully understood. Metallothionein is probably a transport and storage protein for trace elements, such as zinc and copper, that are essential for many physiological functions. Because cadmium is chemically similar to these essential elements, metallothionein can effectively detoxify cadmium by binding with it, but metallothionein enables the body to efficiently store cadmium until it becomes a problem.

When cadmium is combined with metallothionein, it is less toxic to many target organs. Injections of cadmium-bound metallothionein did not cause testcular damage in animals while a similar dose of cadmium chloride did.

However, cadmium-bound metallothionein is more toxic to the kidney than is cadmum chloride (Nordberg 1971). This is in part explained by the fact that most free cadmium is taken up by the liver and only a small percentage (10%) is found in the kidney whereas about 90% of the metallothionein bound cadmium ends up in the kidney. Since metallothionein is freely filterable by the glomerulus and is then actively reabsorbed from tubular fluid, high levels of free cadmium are likely to occur in the tubular cells following degradation of the metallothionein protein. The lack of sufficient new unbound metallothionein to bind with free cadmium allows the latter to produce a toxic effect on the cells. This is similar to the mechanism proposed for renal toxicity following chronic exposure to cadmium.

VI. Acute Health Effects

Cadmium has a moderately acute toxicity with a oral LD_{50} in rats that varies from 72 to over 225 mg/kg depending on the chemical form (see Table VI-1). The toxic effects observed in humans differ depending on whether the route of acute exposure is via ingestion or inhalation. Symptoms in humans following ingestion of acutely toxic levels of cadmium include persistent vomiting, increased salivation, choking sensation, abdominal pain, tenesmus, and diarrhea (EPA 1980a). These symptoms may occur within 15 to 30 minutes of ingestion.

Exposure to acutely toxic airborne concentrations of cadmium (see Table VI-1) may produce symptoms in humans within 4 to 6 hours that include cough, shortness of breath, and tightness of the chest. Acute pulmonary edema may follow within 24 hours. From 3 to 10 days after exposure, proliferative interstitial pneumonitis may occur. In rats a fourth stage occurs which involves permanent lung damage in the form of perivascular and peribronchial fibrosis (EPA 1980a).

Both routes of exposure have led to systemic signs of toxicity that include renal and liver toxicity in both humans and experimental animals. Animal studies have also indicated that acute exposure to high levels of cadmium can lead to testicular and placental necrosis and other reproductive effects. Reproductive effects are further discussed in Section VII.I.

Table VI-1

Selected Acute Toxicity Data[a]

Compound	Species	Route	Effect[b]	Dose
Cadmium (colloidal)	Rat	Oral	LD_{50}	225 mg/kg
Cadmium chloride	Rat	Oral	LD_{50}	88 mg/kg
Cadmium fluoroborate	Rat	Oral	LDLo	250 mg/kg
Cadmium fluorosilicate	Rat	Oral	LDLo	100 mg/kg
Cadmium oxide	Rat	Oral	LD_{50}	72 mg/kg
Cadmium oxide	Rat	Inhalation	LCLo	10 mg/m^3
Cadmium oxide fumes	Rat	Inhalation	LC_{50}	500 mg/m^3/10 min
Cadmium	Human	Inhalation	LCLo	39 mg/m^3/20 min
Cadmium oxide fume	Human	Inhalation	LCLo	2500 mg/m^3[c]
Cadmium oxide fume	Human	Inhalation	TCLo	8.6 mg/m^3/5 hour

[a] Source: NIOSH 1984b

[b] LD_{50} - dose that is lethal to 50 percent of the experimental population
LDLo - lowest dose to produce a lethal effect in the experimental population
LCLo - lowest airborne concentration to produce a lethal effect in humans or in the experimental population
LC_{50} - airborne concentration that is lethal to 50 percent of the experimental population
TCLo - lowest dose to produce a toxic effect in humans or in experimental populations

[c] Although the dose was given in NIOSH (1984b) as 2500 mg/m^3, the actual reported dose was 2500 minutes x mg/m^3 Barrett and Card (1947) estimated that the lethal concentration was 2900 minutes x mg/kg. For an 8 hour work day the airborne concentration would be 5 mg/m^3 and for a 24 hour period the airborne concentration would be 2 mg/m^3.

VII. Subacute and Chronic Health Effects

A. Cardiovascular Effects

Cadmium has been found to induce hypertension and myocardial changes in experimental animals. Friberg et al. (1974) and EPA (1981) have reviewed the literature on these responses in experimental animals and humans. The hypertensive effect of cadmium occurs after chronic low-level oral exposure, but a transient hypertensive reaction can be induced by an acute parenteral administration. Perry et al. (1977) found that exposure through drinking water containing 0.1 to 5 ppm cadmium induced hypertension in rats that were exposed for 18 months. An exposure level of 0.01 ppm had no effect and high exposure levels of 10 and 25 ppm did not have a hypertensive response. The mechanism behind this reaction has not been determined, but may be related to renal toxicity or to an effect on the vasculature. Zinc antagonizes this effect of cadmium.

Cadmium exposure was also found to affect the electrocardiogram recordings of rats treated for 24 weeks with drinking water containing 5 mg of cadmium/liter. Biochemical changes were noted in the myocardium of rats treated with cadmium drinking water concentration as low as 1 mg/liter (Kopp et al. 1978, 1983).

Epidemiological studies have not found a statistically significant association between cadmium exposure and hypertension. Inskip et al. (1982) reported nonsignificantly elevated SMRs for hypertensive deaths

for residents in a town with high soil cadmium content while the control town had a deficit of such deaths. The rate ratios were greater than two for males, females, and both sexes combined. In another epidemiologic study which reported on hypertensive deaths among cadmium-exposed workers, Armstrong and Kazantzis (1983) observed no deaths (.7 expected) in the "ever high" exposure group and a nonsignificant increased risk in the "ever medium" (SMR=178) and the "always low" groups (SMR=113). While these results are suggestive, they do not permit any generalization.

Cerebrovascular deaths were significantly elevated among females in the exposed town from the study of Inskip et al., but deaths from this same cause were reduced in all exposure categories in the study by Armstrong and Kazantzis (significantly so for those with "always low" exposures). Cadmium does not appear to increase the risk of cerebrovascular death.

B. Endocrine Effects

There is some evidence from experimental animal and human studies suggesting that cadmium can affect on endocrine organs (EPA 1981). As will be discussed in Section VII.I, cadmium can cause testicular necrosis at high doses. Since Leydig cells, the androgen producing cells in the testes, are damaged, testosterone synthesis is decreased or abolished until tissue regeneration occurs.

As noted above, the pancreas accumulates cadmium. Glucose intolerance and reduced levels of circulating insulin are associated with cadmium

exposure. Insulin secretion was decreased in rats given intraperitoneal injections of 0.5 mg/kg every other day for 70 days. A dose level of 0.25 mg/kg had no effect (Ithakissios et al. 1975). Selenium and cadmium pretreatment have been found to antagonize this effect.

Cadmium has also been shown to increase adrenal gland weight, adrenal secretion of catecholamines and corticosterone plasma levels in experimental animals. These effects occurred following repeated parenteral administration of doses of 0.25 mg/kg or more of cadmium (Rastogi and Singhal 1975: Der et al. 1977).

Similar dose levels have been associated with decreased plasma T_4 and T_3 levels. There were no morphological changes observed in the thyroid to associate with the plasma level changes (Der et al. 1977).

Repeated intramuscular injection of 250 μg of cadmium chloride for 54 days caused a significant decrease in rat pituitary weight (Der et al. 1977). Some effects observed in the pituitary may, however, be secondary to other endocrine effects caused by cadmium.

C. Hepatic Effects

Several investigators have reported hepatotoxicity in experimental animals exposed to cadmium over long time periods. Rabbits given a 0.25 mg/kg dose of cadmium by injection five days a week for up to 29

weeks had an increase in serum glutamic-oxaloacetic-transaminase (GOT) actively after 17 weeks of exposure (Axelsson and Piscator 1966). At a subcutaneous dose level of 2 mg/kg, 6 days a week for 2 weeks, rabbits had increased serum GOT and glutamic pyruvic-transaminase activities and there were morphological changes in the liver (Kimura 1971). Morphological liver changes without changes in liver function tests, have been reported by Stowe et al. (1972) in rabbits given drinking water containing 160 ppm cadmium for 6 months. Some liver enzyme changes have occurred in rats treated with cadmium via drinking water at 1 ppm (Sporn et al. 1970).

Pronounced changes in liver function are unusual findings in cadmium exposed workers, however, this has not been a major focus of most epidemiological studies (Friberg et al. 1974).

D. Mineral Metabolism

Chronic exposure to cadmium has an adverse effect on calcium and phosphorus metabolism manifested through an observed effect on bone. Bone changes in rats given drinking water containing 50 ppm cadmium had reduced urinary calcium and phosphorus levels and fat deposition in the femoral spongiosa. Treated animals on a calcium deficient diet had thinning of the cortical osseous tissue, osteoid borders on trabeculae, and a decreased number of osteocytes, and a decrease of acid mucopolysacchrides in epiphyseal cartilage (Itokawa et al. 1974). Osteomalacia and severe osteoporosis in humans have been associated with both occupational and environmental exposure. These are the most

prominent effects of Itai-Itai disease. Patients with this disease generally have hypochronic anemia and renal disfunction (proteinuria, glucosuria, and aminoaciduria) as well as skeletal abnormalities. The disease has been confined primarily to a Japanese population (mostly post-menopausal women) residing in an area that is highly contaminated with cadmium. Although the average daily lifetime cadmium intake is not known, the highest intake estimates are over 1 mg/day for at lease part of their lifetime. The disease is believed to be caused by cadmium's renal toxicity disturbing calcium and vitamin D metabolism, but there is evidence that calcium and vitamin D deficiencies may play an etiological role.

E. Hematological Effects

Cadmium does not appear to have strong effects on the hematopoietic system, although animal studies have indicated cadmium can induce a reduction in hematocrit and hemoglobin levels of chronically exposed experimental animals (EPA 1981). Administration of supplemental iron has restored hemoblogin and hematocrit levels. Friberg et al. (1974) reviewed a few epidemiological studies on cadmium-exposed workers where it was found these workers had a moderate anemia.

Decker et al. (1958) found that rats given drinking water containing 0.5 to 1 ppm cadmium for 1 year had normal hemoglobin levels while rats given drinking water containing 50 ppm cadmium for 3 months had low hemoglobin levels. Mahaffey et al. (1981) report that rats fed a diet containing 50 ppm of cadmium for 10 weeks had reduced bone, kidney, and

liver iron levels, suggesting that cadmium may have an affect on iron metabolism.

F. Immunological Effects

Cadmium has been found to decrease the number of antibody-forming spleen cells in mice exposed subchronically via drinking water to 3 or 300 ppm (Koller et al. 1976). In an unplanned study, it was noted that mice being treated with cadmium at 3 and 300 ppm in their drinking water had a higher mortality following an accidental intestinal infection from Hexomita muris than did untreated mice (Exon et al. 1975). Cadmium has also been found to decrease thymus and spleen weights of mice injected with doses of 0.75 to 6 mg/kg. There was also suppression of the induction of delayed hypersensitivity responses and decreased memory T-cell and B-cell activities (Kojima and Tamura 1981).

G. Respiratory Effects

Emphysema and bronchitis are the primary respiratory effects reported from chronic inhalation exposure to cadmium. A causal relationship was first reported by Friberg (1950) who noted this effect in workers exposed to cadmium oxide dust. Since then the results of several epidemiological studies on cadmium-exposed worker populations have confirmed this finding. Several animal studies provide supporting evidence that cadmium causes emphysematous type changes in the lungs. These studies have been reviewed by Friberg et al. (1974) and EPA (1981).

Friberg (1950) exposed rabbits to cadmium iron oxide dust at an airborne concentration of 8 mg/m^3 for 3 hours per day, 20 days per month over an eight-month period. All exposed rabbits showed signs of emphysema and inflammatory changes. Prigge (1978) exposed rats to cadmium oxide at a much lower airborne concentration--25 to 50 μg/m^3 (as cadmium)--24 hours a day for 90 days. Emphysematous areas and cell proliferation of the bronchi and bronchioli were found in all of the exposed animals. This finding, however, is in contrast to the absence of reported emphysematous changes in rats exposed to cadmium chloride at concentrations of 13 to 51 μg/m^3 (as cadmium)--23.5 hours per day for 18 months and then followed for an additional 13 months (Takenaka et al. 1983).

Two reports indicated that rats given cadmium (17.2 mg/liter) in their drinking water for up to 10 months developed emphysematous changes (Miller et al. 1974, Petering et al. 1979). Petering et al. (1979) reported that supplemental zinc in the animals' diet decreased the severity of the changes.

Human studies have, for the most part, been done in the occupational setting. A large number of these studies, reviewed by Friberg et al. (1974) have shown that there are significant changes in pulmonary function tests in groups of exposed workers. Many of these studies did not control for smoking. Since cigarette smoke contains significant amounts of cadmium and there is an association between smoking and emphysema and bronchitis, Friberg et al. suggest that there is reason to believe that smoking may be of importance. Friberg et al. also

observe that, "For cadmium oxide fumes, a prolonged industrial exposure to below 0.1 mg/m^3 might well be considered hazardous with reference to emphysema."

Human studies of the effect on respiratory disease mortality are not consistent. The two findings which were statistically significant were those by Varner (1983) who found a PMR (proportional mortality ratio) of 153 for nonmalignant respiratory disease, and by Armstrong and Kazantzis (1983) who found an increased risk for bronchitis standardized mortality ratio or SMR = 434 for those with "ever high" exposure, SMR = 130 for entire cohort. There was a dose-response relationship with both intensity and duration of exposure, though other exposures may also have played a role. The SMR for nonmalignant respiratory disease showed a nonsignificant but elevated risk in the early cohort of Lemen et al. (1976) (SMR = 159) and in the followup by Thun et al. (1985) (SMR = 154), but these are only modified versions of the cohort Varner studied. Andersson et al. (1984) noted two lung disease deaths with unusual diagnoses that were considered potentially related to cadmium exposure.

Negative findings were reported by Andersson et al. (1984), and Sorahan and Waterhouse (1983). This latter study showed a lower SMR (107) for men employed earlier (when exposures were higher) than for those employed later (128). The ecological study by Inskip et al. (1982) of a town with high cadmium soil content showed extreme deficits (statistically significant) for "all respiratory diseases", in comparison to all of England and Wales, and also in comparison to a

similar nearby town with no exposure to cadmium. However, the exposure in this town was believed to be by ingestion of food grown in contaminated soil, rather than by inhalation.

In an epidemiological study not reviewed by Friberg et al. (1974), workers from different factories, an electronic workshop, a nickle-cadmium storage battery factory, and two cadmium-producing plants, were used to examine pulmonary effects (Lauwerys et al. 1974, 1979). Control groups for each factory were selected and matched according to sex, age, weight, height, smoking habits, and socio-economic status. Two groups of exposed male workers were formed. One group consisted of workers who had been was exposed to cadmium dust and fumes for less than 20 years with an average length of 7.5 years. The second group was made up of workers who had been exposed an average 27.5 years primarily to cadmium oxide fumes. The highest respiratory dust levels (undefined) measured in these factories ranged from 21 to 65 $\mu g/m^3$. Both exposure groups had statistically significant decreases in spirometric indices of forced vital capacity, forced expiratory volume in one second, and peak expiratory flow rate compared to the respective controls. These changes were considered to indicate a mild form of obstructive lung disease.

In a second study, Lauwerys et al. (1979) did a more detailed lung function test on a group of 18 cadmium workers with more than 20 years (average 32 yrs) of exposure. At the time of the study measured total airborne cadmium ranged from 3 to 67 $\mu g/m^3$, but some workers may have been exposed to levels higher than 350 $\mu g/m^3$ prior to 1970. The only

statistically significant changed compared to matched controls was in closing capacity. Although a number of parameters indicating obstructive lung disease were found to differ from control values, the changes were not statistically significant. The authors conclude that the functional impairments observed from chronic cadmium inhalation exposure are only slight compared to the renal effects that were also studied.

A group of non-smoking female workers with an average exposure period of 4.4 years at total airborne cadmium concentration of 10 $\mu g/m^3$ (4 $\mu g/m^3$ respirable dust level) was also examined by Laurwerys et al. (1979). There were no significant lung function changes found for the exposed group compared to a matched control group. The negative finding may be due to the lower exposure level or shorter exposure period.

Both animal and human studies have found pulmonary effects at airborne concentrations of around 20 $\mu g/m^3$. No effects were found in an animal chronic inhalation study at levels of 13 to 51 $\mu g/m^3$ nor in a human study at an average exposure level of 4 $\mu g/m^3$ for an average of 4.4 years.

H. Renal Effects

Cadmium-induced renal toxicity has been found in experimental animals and in both occupationally and nonoccupationally exposed populations. This effect has received the greatest amount of attention because it has been determined to be one of the most sensitive adverse effects

caused by chronic cadmium exposure (Friberg et al. 1974: EPA 1981). The literature on renal toxicity has been reviewed by Friberg et al. (1974), Kawai et al. (1976), and EPA (1981). Because this effect has been so well-documented, the following discussion will just briefly describe cadmium-induced renal toxicity, the postulated mechanism, and levels of cadmium needed to induce this effect.

The earliest clinical sign of cadmium induced renal toxicity is proteinuria, which occurs in both experimental animals and humans (Friberg et al. 1974). The increase in protein excretion is believed to be related to renal tubular damage caused by cadmium which interferes with protein reabsorption from tubular fluid, a metabolically active process. The early stage of this proteinuria is characterized by the relatively large increase of low molecular weight proteins and the relatively small increase of large proteins like albumin that are excreted and is classified as tubular proteinuria. Clinically, the low molecular weight protein β_2-microglobulin is used as a marker for this type of proteinuria. Once damage occurs, followup studies of workers indicate proteinuria does not decrease even after exposure ends. Thus, renal damage appears irreversible (Piscator 1983). Other signs of renal dysfunction are glucosuria and aminoaciduria, although these usually occur later than proteinuria or following exposure to higher levels of cadmium. An increased incidence of renal stones has also been reported in cadmium workers (Friberg et al. 1974).

Cadmium-induced proteinuria has occurred without detectable morphological changes in the kidneys. However, severe pathological changes do occur with chronic cadmium toxicity. These changes are primarily in the proximal tubules, which can appear grossly atrophied or dilated with the epithelium flattened. There are also changes in the vasculature and ischemic atrophy of glomeruli (Bonnell 1955).

The mechanism of renal tubular damage is believed to be an overload of the detoxification mechanism for cadmium in the kidney (Friberg 1984). As noted in Section V.E, much of the cadmium that accumulates in the kidneys is in the form of cadmium-bound metallothionein, which is freely filtered through the glomerulus and then reabsorbed by the tubular cells like other low molecular weight proteins. Reabsorption via pinocytosis results in cadmium-bound metallothionein accumulation in the lysosomes, where the protein is catabolized and the cadmium ion is released. Free cadmium is normally and rapidly bound to new metallothionein. Toxicity results when the kidneys can no longer produce sufficient metallotheionein to bind excess free cadmium. An early toxic effect is on the reabsorption process of low molecular weight proteins which results in tubular proteinuria. Histopathological changes in the vasculature of affected kidneys may also be due to free cadmium, since cadmium has been found to affect the vasculature in other organs, such as the testes and placenta.

A dose-response relationship for cadmium-induced renal toxicity, has been determined by working backwards from the tissue concentration at which toxicity occurs. This is a reasonable approach since the

biological half-life of cadmium is approximately 10 to 30 years (Friberg et al. 1974).

Several animal studies have shown that morphological changes and/or proteinuria occurred with kidney concentrations of 150 to 225 μg/g wet weight (Kawai et al. 1976, Nomiyama 1975, Suzuki 1975). Friberg et al. (1974) proposed that 200 μg/g wet weight of kidney cortex was the "critical concentration" based on limited human autopsy data. The critical concentration was never explicitly defined but appears to be the average concentration at which an effect was observed. WHO (1977) agreed with this estimate, but gave a range of 100 to 300 μg/g. Nomiyama (1977) suggested that 200 μg/g wet weight is too low of an estimate because Friberg et al. included cases who had morphological changes. Morphological changes could indicate loss of cadmium from the tissue since dead tubule cells containing cadmium would be sloughed off and excreted in the urine. Lower renal cortex cadmium levels were found in cases with pathological changes compared to cases that only had proteinuria.

More recent attempts to correlate renal cortex concentration to renal toxicity have compared the degree of proteinuria to renal cadmium levels determined by the in vivo measurement technique of neutron activation (Roels et al. 1979, 1981, 1983, Ellis et al. 1981). This is a noninvasive method that allows tissue measurements of cadmium in healthy subjects. Unfortunately, there have not been studies comparing this technique to those of conventional analytical techniques (Friberg 1984). However, it was believed by Friberg, Kjellström, and Elinder to

be sufficiently accurate to determine the critical concentration (Kjellstrφm et al. 1984).

Kjellstrφm et al. (1984) evaluated the approaches used by Roels et al. (1981) and Ellis et al. (1981) to estimate the critical concentration, incorporating data generated in these studies to expand the concept of "critical concentration" to include the expected population response rate designated the "population critical concentration" (PCC) (Friberg and Kjellstrφm 1981). The latter is similar in concept to the LD_{50} (lethal dose to fifty percent of a population), so that a critical concentration that is expected to affect 10 percent of a population would be noted as PCC-10. This new concept is more useful than the critical concentration in assessing the risk posed to a population. Kjellstrφm et al. (1984) estimated that the PCC-50 is about 250 to 270 μg Cd/g wet weight of renal cortex and the PCC-10 is about 180 to 220 μg Cd/g wet weight of renal cortex.

Friberg et al. (1974) estimated the necessary daily retention of cadmium to achieve a renal cortex cadmium concentration of 200 μg/g wet weight based on mathematical models that they had developed. Daily retention values were estimated for exposure periods of 10, 25, and 50 years assuming various biological half-lives of cadmium. The assumed half-lives ranged from infinite retention to 9.5 years with a 19 year half-life considered to be most plausible by Friberg et al. . Table VII-1 lists daily cadmium retention values estimated to achieve a renal cortex concentration of 200 μg/g wet weight. Using these values

Friberg et al. (1974) estimated ambient air concentrations necessary to reach the critical concentration in a 10, 25, or 50 year exposure period. Absorption from the lungs was considered to be 25 or 50 percent (See Section V.A). These ambient air concentrations are listed in Table VII-2. For a 50 year exposure period, assuming 50 percent lung absorption and a 19 year biological half-life, the corresponding ambient air level is 1.5 $\mu g/m^3$. Using a similar exposure period and biological half-life, the minimum daily cadmium intake from food or smoking was estimated to be 350 μg/day and 286 cigarettes/day (0.1 μg cadmium per cigarette), respectively. All of these values are independent of each other. Therefore, if ingestion accounted for most of the daily cadmium retention, as expected, exposure to airborne cadmium would have to be reduced to keep the overall daily retention the same. Since the PCC-10 value estimated by Kjellstrøm et al. (1984) is similar to the critical concentration originally proposed by Friberg et al. (1974), the daily cadmium intake values estimated by Friberg et al. may be applicable to the PCC-10 risk level.

Table VII-1

Necessary Daily Cadmium Retention (μg) to Reach Renal Cortex Cadmium Concentration of 200 $\mu g/g$ (Wet Weight) under Different Excretion Rate and Exposure Time Alternatives

Exposure time in years	Excretion per day, % of body burden (corresponding biological half-time in years in parentheses)				
	0 (∞)	0.002 (95)	0.005 (38)	0.01 (19)	0.02 (9.5)
10	32.9	34.1	35.9	39.2	46.3
25	13.1	14.4	16.4	20.1	28.6
50	6.6	7.8	10.0	14.3	24.6

Source: Friberg et al. 1974, Table 9:2

Table VII-2

Necessary Cadmium Concentration ($\mu g/m^3$) in Ambient Air to Reach Critical Cadmium Concentration (200 $\mu g/g$ Wet Weight) in Kidney Cortex under Different Absorption, Excretion, and Exposure Time Alternatives (Ventilation = 20 m^3/24 hr)*

Pulmonary absorption (%)	Exposure time in years	Excretion per day, % of body burden (corresponding biological half-time in years in parentheses)				
		0 (∞)	0.002 (95)	0.005 (38)	0.01 (19)	0.02 (9.5)
25	10	6.6	6.8	7.2	7.8	9.3
	25	2.6	2.9	3.3	4.0	5.7
	50	1.3	1.6	2.0	2.9	4.9
50	10	3.3	3.4	3.6	3.9	4.7
	25	1.3	1.5	1.7	2.0	2.9
	50	0.65	0.8	1.0	1.5	2.5

Source: Friberg et al. 1974, Table 9:4

Recently Ellis et al. (1985) reported a study correlating occupational cadmium inhalation exposure to liver and kidney cadmium levels and renal dysfunction. The workers were divided into active and retired categories with normal or abnormal kidney function. Ellis et al. (1985) found a good correlation between the exposure estimates (time-weighted cumulative exposure index) for each worker and liver cadmium levels ($r=0.7$, $p<0.001$). They also found a good correlation between exposure levels and kidney cadmium levels in active workers with normal kidney function ($r=0.83$, $p<0.001$). Active and retired workers with abnormal kidney function tended to have lower kidney cadmium levels, suggesting a loss of cadmium when toxicity occurs. The percentage of workers with abnormal renal function was found to increase with increasing exposure (see Table VII-3). This relationship was examined using linear logistic regression analysis and was found to be best described by the equation:

$$\text{logit } p = 1.24 \ln (\text{TWE}) - 8.34$$

where p is the probability a worker would be classified as having kidney dysfunction, logit p is $\ln (p/1-p)$, and TWE is the cumulative exposure index.

Using this relationship, the cumulative exposure index for a probability of classifying 10 percent of the workers as having abnormal kidney function is about 140 $\mu g/m^3$. This would be equivalent to continuous exposure to an ambient air concentration or 2.8 $\mu g/m^3$ for 50 years or 2.0 $\mu g/m^3$ for 70 years. These values are in close agreement with the

value estimated by Friberg et al. (1974). However, they do not take into account exposure from other sources that would be expected to contribute to the cadmium burden in the kidneys.

Table VII-3

Incidence of Abnormal Kidney Function
in Relation to Exposure Category[a]

Time Weighted Exposure Index (yr x $\mu g/m^3$)	Renal Function Classification		Incidence
	Normal	Abnormal	
≤ 20	9	0	0
20 - 100	9	1	0.10
100 - 500	7	2	0.22
500 - 1000	9	6	0.40
1000 - 3000	6	13	0.68
3000 - 6000	1	12	0.92
> 6000	0	7	1.00

[a] Abnormal kidney function was defined as a urinary β_2-microglobulin concentration of > 200 $\mu g/g$ creatinine or total urinary protein > 250 mg/g creatinine.

Source: Ellis et al. (1985), Figure 4.

I. Reproductive Toxicity

Cadmium has been found to cause a variety of adverse reproductive effects, including gonadal toxicity, decreased fertility, placental toxicity, embryo-and fetotoxicity, teratogenicity, and developmental effects. Many of these effects have been extensively studied in experimental animals and looked for in human populations. Numerous recent reviews have been written on the findings of these studies (Barlow and Sullivan 1982, Carmichael et al. 1982, Ferm and Layton 1981, Bhattacharya 1983, EPA 1981). The summary below will give an overview of these findings and only cite studies that give no observed effect levels or other specific information.

1. Gonadal Toxicity

Testicular Damage: It has been well documented that cadmium induces testicular necrosis in experimental animals given an acute dose by intraperitoneal or subcutaneous injection. Pathological changes start to occur within hours of exposure, progressing to edema, hyperemia, hemorrhage, thrombosis and ultimately necrosis of the interstitial tissue and seminiferous tubules. Along with this tissue damage, there is loss of androgen production, which may account for changes in some accessory sex organs such as the prostate. Cadmium may also have a direct effect on the prostate. Variable recovery of the androgen producing tissue does occur; however, there is no regeneration of the seminiferous tubules.

Testicular damage is generally believed to be secondary to cadmium's effect on the capillary endothelium. Capillary damage causes the micro-vasculature to become obstructed, resulting in tissue ischemia. The damage caused by cadmium can be prevented by simultaneous administration of zinc, selenium, cysteine, estrogen, or by pretreatment with non-toxic doses of cadmium. The antagonistic effects of zinc and selenium may be due to an increased intracellular concentration of these metals that prevents cadmium from being incorporated into essential zinc or selenium enzymes. Cadmium incorporation may reduce or abolish these enzyme activities. Pretreatment of small amounts of cadmium probably induces metallothionein synthesis and therefore less free cadmium is available.

Krasovskii et al. (1976) reported that adverse effects in the testicles of rats given cadmium chloride in their drinking water at a dose level of 0.5 and 5 μg/kg but not at 0.05 μg/kg. EPA (1981) states that these reported findings must be viewed with caution because the high control blood levels of cadmium reported are not consistant with the dose levels and because the doses used are less than those likely to be found in food. Dixon et al. (1976) reported that no gonadal effects occurred in rats given drinking water containing 1 to 100 μg/l (maximum dose 14 μg/kg/day) for up to 90 days. Similarly, Loeser and Lorde (1977) reported that no effects occurred in rats fed diets containing 1 to 30 ppm cadmium chloride. Senczuk and Zielinska-Pauja (1977) did report finding damage to spermatogenic tubules and slight interstitial tissue hypertrophy in rats fed diets containing cadmium chloride at 8 or 88 mg/kg diet (ppm) for 12 to 15 months but not when fed the diets

for 3 or 6 months. The extent of damage to the spermatic tubules could not be ascertained nor could the study be evaluated since the information was reported in an abstract.

Ovarian damage: High doses of cadmium chloride, 3 to 10 mg/kg, given by subcutaneous injection have been reported to cause ovarian hemorrhage in mice and rats. Lower doses of 0.22 and 0.45 mg cadmium/kg produced this effect in immature and mature gerbils. Although ovarian follicles in rats underwent mass atresia following injection, upon recovery new follicles differentiated from primordial oocytes and the ovary appeared histologially normal. The effect was found to be inhibited with simultaneous injection of zinc or selenium. Der et al. (1977) reported that daily intramuscular doses of 50 or 250 μg of cadmium chloride for 54 days did not induce any histological change in ovaries of treated rats even though a persistent diestrus was seen in the high dose animals.

2. Fertility

Following cadmium-induced testicular atrophy, there is regeneration of the interstitial tissue. However, there is little or no regeneration of spermatogenesis, so that infertility has been observed in several studies. At a dose, 1 mg/kg by intraperitoneal injection, that caused little or no histopathological effect in the testes, a study in mice indicated that fertility can be reduced, but recovery is possible (Lee and Dixon 1973).

The effect of cadmium on the fertility of females has not been well-studied. Only one study (Sutou et al. 1980) suggested that females given an oral dose of 10 mg/kg/day for three weeks had reduced fertility. Doses of 0.1 and 1 mg/kg/day had no effect. In this study the males were also treated, but, when mated with untreated females, no effect on fertility was observed at any dose level.

3. Placental Toxicity

Cadmium has been shown to induce acute hemorrhagic necrosis of the placenta in laboratory animals given high doses (>1 mg/kg) by systemic injection. Toxicity is believed to be due to cadmium's effect on the vasculature of the placenta, producing ischemia in the tissue similar to the effect found in the testes. Cadmium may also be directly toxic to placental tissue (Di Sant'agnese et al. 1983).

4. Embryo and Fetotoxicity and Teratogenicity

Cadmium is fetotoxic: exposure to levels as low as 8 ppm in the diet or 600 $\mu g/m^3$ in the air throughout pregnancy induced a decrease in body weight and hemoglobin levels of fetal or newborn rats. Following parenteral administration of cadmium at dose levels of around 1 mg/kg, an increase in the percentage of resorptions per litter was observed. Large doses of cadmium produce rapid fetal lethality due to cadmium's placental toxicity.

In addition to causing fetal toxicity, cadmium is also teratogenic. This effect has been observed in an extensive number of studies on a variety of laboratory rodent species, as well as in a few studies on birds, fish, and amphibia. The major abnormalities reported to occur in rodents are cleft palate, limb defects, incompletely developed lung, and CNS defects, such as hydrocephalus and exencephalus.

The dose of cadmium required to induce malformations in rodents has been in the range of 0.6 to 5 mg/kg given parenterally during the period of organogenesis. Ishizu et al. (1973) reported that a subcutaneous injection of 0.63 mg/kg cadmium on day 7 of pregnancy induced a small number of malformations in mice; however, a dose of 0.33 mg/kg did not induce such effects. Nolen et al. (1972a) reported an increase in malformations in rats orally treated with cadmium at 4 mg/kg from days 6 to 14 of gestation, but not when treated at dose levels of 0.01 mg/kg. However, this finding of malformations could not be replicated in a second study (Nolen et al. 1972b).

Cadmium fetotoxic and teratogenic effects have both been found to be antagonized by simultaneous administration of zinc or selenium. Pretreatment with low doses of cadmium have also decreased the fetolethality and teratogenicity of cadmium. This latter effect is probably due to induction of metallothionein, which then detoxifies the later dose of cadmium.

5. Developmental Effects

Animals studies have indicated that developmental effects occur following exposure during gestation, including decreased weight gain, depressed spontaneous activity and other neurobehavioral deficits. One explanation for these effects is that some essential elements, such as zinc, copper and iron, are inhibited from crossing the placenta by cadmium (Carmicheal et al. 1982).

6. Human Reproductive Effects

Few studies have dealt with cadmium's effect on human reproduction. Smith et al. (1960) reported on the histopathology of testes in an autopsy series of five cases with work histories of intermittent occupational exposure to cadmium fumes ending 5 to 19 years before death. The testes were found to be microscopically normal; however, low levels or an absence of spermatids and spermatozoa were observed microscopically. The authors suggested the effects on spermatids and spermatozoa were due to the terminal illness and not cadmium exposure. Favino et al. (1968) reported that one of ten male workers manufacturing nickel-cadmium storage batteries was impotent but no conclusion can be drawn from this anecdotal report.

Tsvethkova (1970) reported that children born to women working in an alkaline battery factory and a zinc molding factory, where cadmium

exposures ranged from 0.1 to 25 mg/m^3 and 0.02 to 25 mg/m^3, respectively, had significantly lower birth weights than an unexposed control group. Four of 27 children born to women working in the zinc molding factory were reported to be born with clear signs of rickets. The details provided in the study are not sufficient to evaluate these results (Barlow and Sullivan 1982).

7. Conclusion

Animal studies have shown that cadmium can have multiple effects on reproduction. It is toxic to the gonads and placenta and can cause fetotoxicity and teratogenicity. Adequate human evidence of reproductive toxicity is lacking and a no-observed-effect-level (NOEL) cannot be estimated from human data. Animal data would suggest the NOEL to be no greater than 100 μg/kg/day. This would be equivalent to an airborne concentration of about 330 μg/m^3. Even when safety factors are included to take into account population and species variability, and exposure duration, the ambient exposure level is below what might reasonably be considered a safe exposure level for reproductive toxicity.

J. Carcinogenic Effects

1. Mutagenicity

The mutagenic potential of cadmium has been examined using a variety of methods and test systems. Prokaryotic systems have been used to assess

gene mutation and reparable genetic damage caused by cadmium. Gene mutation has also been studied in yeast, Drosophila, and mammalian cells. In vitro and in vivo work has been done to assess the role of cadmium in inducing chromosomal aberrations in mammalian systems including humans. Many of these studies have recently been reviewed and evaluated by EPA (1985). The following discussion summarizes the general findings from these studies.

Using Salmonella typhimurium tester strains, several studies have indicated that inorganic cadmium salts do not induce gene mutations. A positive response was observed in one study where cadmium diethylthiocarbamate was tested (Hendenstedt et al. 1979). This effect occurred at only one of the intermediate concentrations used, so no dose-response relationship was observed. However the effect occur at that concentration in two different tester strains. Zinc diethylthiocarbamate was also mutagenic in this study, suggesting that diethylthiocarbamate and not cadmium was the mutagenic moiety. The results of two studies using the Bacillus subtillis rec-assay indicate that cadmium in soluble inorganic salts is weakly mutagenic in that system (Nishioka 1975, Kanematsu et al. 1980). Cadmium was also found to act synergistically with a potent mutagen, N-methyl-N-nitro-N-nitrosoguanidine, in the S. typhimurium test system (Mandel and Ryser 1981).

Cadmium chloride was reported to produce a positive mutagenic response in the yeast Saccharomyces cerevisiae (Takahashi 1972). However, this effect was weak and did not follow a dose-response relationship. In

addition, one endpoint, petite mutations, involve mitochondrial DNA and not nuclear DNA.

Positive mutagenic responses have been reported for cadmium chloride and cadmium sulfate when tested in the mouse lymphoma L5178YTK+/- assay system. This effect occurred in a dose-related manner at cadmium concentrations between 10^{-7} and 10^{-6}M (Oberly et al. 1982). Other mammalian cell test systems have also been reported to show weakly positive mutagenic activity when soluble cadmium salts were used.

A number of studies have been conducted with Drosophila melanogaster as the test organism, using different endpoints to test cadmium mutagenicity. Most test results were considered negative (Sorsa and Pfeifer 1973, Sabalina 1968, Ramel and Magrusson 1979, Inone and Watanabe 1978). The results reported for one study, however, indicated that cadmium chloride induced an increased frequency of dominant lethal mutations (Vasudev and Krishnamurthy 1979).

Cadmium's ability to induce chromosomal aberrations has been studied in in vitro systems using human cells and other mammalian cell lines with mixed results. Cadmium sulfide was reported to have induced a large number of chromosomal aberrations in human lymphocytes in one study (Shiraishi et al. 1972). This study has been criticized because the cells came from only one donor, only one concentration of cadmium was used, the solvent used for the insoluble cadmium compound was not stated, and only a limited number of cells were examined. A second study was also reported to have been positive using human lymphocytes

exposed to cadmium acetate over a concentration range of 4 orders of magnitute (Gasiorek and Barichinger 1981). Although there was a dose-related increase in chromosomal gaps, the increase in structural aberrations was not dose-related. Other studies with human lymphocytes using similar concentrations were reported to be negative.

Soluble cadmium salts have been reported to induce chromosomal aberrations in other cultured mammalian cells at concentrations similar to the ones that caused this effect in human lymphocytes. Rohr and Bauchenger (1976) found that cadmium sulfate induced numerical chromosomal aberrations in the Chinese hamsters cell line "Hy" by interfering with spindle function. Cadmium chloride induced chromosomal aberrations in cultered Chinese hamster ovary cells when grown in the presence of bovine serum but not when the bovine serum in the media was replaced by fetal calf serum (Deaven and Campbell 1980). This suggests the culture media used can influence the outcome of a study.

As in the other test systems, results from in vivo animals studies on cadmium mutagenicity and clastogenicity have been mixed. Several mutagenicity studies looking for dominant lethal effects in rats gave negative results. However, dominant lethal assays are relatively insensitive for detecting all types of mutagens (Russel and Matter 1980). On the other hand, several studies showed that cadmium treatment induced nondisjunction in oocytes and blastocytes of experimental animals. Cadmium chloride did not induce chromosomal aberrations nor

increase the frequency of micronuclei in bone marrow cells of treated mice.

A number of studies have examined whether occupational or environmental exposure to cadmium increased the number of chromosomal aberrations found in human blood lymphocytes. Two out of six studies reviewed by EPA (1985) reported significant increases. One of the positive studies had been on Itai-Itai patients, but a negative study was also reported in Itai-Itai patients (Shiraishi 1975, Bui et al. 1975). Patients from the negative study had not been given drugs or x-rays while the cohort of the positive study was not controlled for these factors, which can seriously influence the results of this type of study. The cohort from the other positive study had been occupationally exposed to cadmium and other metals. These other metals may also have had an effect.

Although not all genotoxicity studies on cadmium were positive, the results of several studies on mammalian and bacterial gene mutation and chromosomal aberrations in-cultured mammalian cells and intact animals that suggest that cadmium is mutagenic. However, a definitive conclusion cannot be made until the bases for discrepancies in results of similar studies are better understood.

In summary, bacterial test systems have given conflicting results. Inorganic cadmium salts failed to induce reverse mutations in Salmonella typhimurium tester strains used in an Ames assay system; however, they were found to be weakly mutagenic to Bacillus subtilis strains used in the rec-assay system. The discrepancy could be from

species or assay system differences. Soluble cadmium salts were weakly mutagenic in a number of studies using mammalian cells. Although the high concentration of cadmium proved to be toxic in some studies, positive findings were obtained when cell survival was considered adequate. Only one of a number of mutagenicity studies using Drosophila melanogaster reported positive findings. In vivo animal mutation studies have been negative, but these studies are relatively insensitive.

Mixed results were found in studies that examined cadmium's ability to induce chromosomal aberrations in cultured animal and human cells. One study indicated that cadmium may cause some aberrations by interfering with spindle function. Results of another study suggest that culturing conditions could significantly affect the results and thus make it difficult to draw any conclusions from these in vitro studies on chromosomal aberrations. In vivo animal studies have produced mixed results. The positive findings indicated that cadmium affected spindle function. These findings in vivo correlate with the findings of one in vitro study. Although an increase in chromosomal aberrations has been found in two studies on lymphocytes taken from exposed humans, confounding factors may have affected the validity of these results.

The information reviewed suggests that cadmium may induce mutations and chromosomal aberrations. However, this evidence is limited and in a number of cases there are conflicting results. Therefore, at this time the staff of DHS regards the evidence of genotoxicity as suggestive but inconclusive.

2. Carcinogenicity

Animal Studies

Cadmium has been the subject of numerous studies in experimental animals to determine its carcinogenic potential. Many of these studies involved subcutaneous or intramuscular injection, others oral administration, and several recent studies have involved intratracheal injection or inhalation of an aerosol. These studies have been extensively reviewed elsewhere (IARC 1973, 1976; EPA 1981, 1985; Sunderman 1977) and for the most part will only be briefly discussed here.

Injection Studies

Most studies in which rats were given subcutaneous or intramuscular injections of a cadmium compound found that injection site tumors formed. The cadmium compounds used were primarily soluble inorganic cadmium salts, but insoluble cadmium salts and cadmium metal powder were also effective in inducing tumors. The tumors that were formed were sarcomas, which are the most common type of injection site tumor. Induction of injection site sarcomas can indicate a compound is carcinogenic, but the studies are not useful for quantitative evaluation of the compounds carcinogenic potential because of the atypical route of exposure. The vast majority of injection route studies have been in rats and only a small number of mouse studies have been reported. Injection site tumors have not been seen in the few studies conducted with mice.

Although injection site tumors were not found in mice, in one study a high incidence of interstitial-cell tumors of the testis was found in treated mice, while no such tumors were found in control animals (Gunn et al. 1963). Tumors formation followed cadmium-induced testicular damage and tissue regeneration. Similar findings of a high incidence of interstitial-cell testicular tumors were also reported to have occurred in a number of rat studies (Gunn et al. 1964; Levy et al. 1973; Poirier et al. 1983). In a recent study (Poirier et al 1983), rats given a subcutaneous injection of cadmium chloride were found to have a significantly increased incidence of pancreatic islet cell tumors (3 of 137 control, 22 of 259 treated; $p<0.02$). This is of interest because the pancreas is one of the tissues found to accumulate cadmium.

In two studies Gunn et al. (1963,1964) injected rats with zinc acetate at the same site as cadmium chloride but at 100 times the dose. They found that zinc decreased the incidence of local and interstitial cell testicular tumors. Poirier et al. (1983) found that magnesium acetate injected at the same site as cadmium chloride at 300 to 600 times the dose inhibited formation of local tumors but did not have a noticeable effect on the induction of testicular tumors.

Oral Administration

Several of chronic studies have been conducted in which soluble cadmium salts were administerd to mice or rats via their drinking water or diet or by gavage. None of these studies indicated that cadmium was

carcinogenic. The most adequate studies conducted include those done by Levy and Clack (1975) and Levy et al. (1975) who examined the carcinogenicity of cadmium sulfate in rats and mice, respectively. Groups of 50 male rats were given weekly oral doses of 0.087, 0.18, or 0.35 mg cadmium sulfate/kg for a two year period. No increase in tumor incidence was observe. Groups of 50 male mice were given weekly oral doses of 0.44, 0.88, or 1.75 mg cadmium sulfate/kg. No increase in tumor incidence compared to the control group was observed in this study. The primary objective of these studies was to investigate prostate cancer and therefore the number of tissues examined was limited. In addition the rat strain used has a normal high lifetime incidence of spontaneous interstitial cell tumors which makes it very difficult to observe an increase in this type of tumor.

EPA (1985) evaluated an unpublished FDA (1977) study. Groups of 26 to 32 male and 26 to 29 female Charles River rats were given diets containing 0, 0.6, 6, 30, 60, 90 ppm cadmium chloride for 103 weeks. No increase incidence of any tumor was found. These levels of cadmium did not have an effect on survival, although electron microscopy revealed some changes in the kidneys.

Loeser (1980) also conducted a two year carcinogenic bioassay in rats. Groups of 50 male and 50 female Wistar rats were given cadmium chloride in their diets at concentration of 0, 1, 3, 10, or 50 ppm cadmium. The only statistically significant effect was a reduction in body weight of the high dose male group.

Inhalation and Intratracheal Administration

Sanders and Mahaffey (1984) examined the carcinogenic potential of cadmium oxide in male rats by intratracheal instillation. The rats were treated one, two or three times with 25 μg of cadmium oxide. The first administration was given at 70 days of age and then at 100 and 130 days of age depending on the total dose to be given. i.e. 25, 50, or 75 μg. The animals were then followed for their lifetime. No differences were found in survival times or organ weights between treated and control groups. Using life-table and contingency table statistical analyses a significant increase in benign mammary fibroadenomas was observed in the high dose group. Additionally, there was a significant increase in the number of rats in the high dose group that had three or more tumor types.

Hadley et al. (1979) exposed a group of 61 male Wistar strain rats one time to an airborne cadmium oxide aerosol concentration of 60 mg/m^3 for 30 minutes. The mass median diameter of the particles was 1.4 μm with a geometric standard deviation of 1.9 μm. Seventeen animals were used as controls. Twenty-seven exposed animals died within three days from acute pulmonary edema. The remaining animals were then observed for one year. No morphological changes were noted in the lungs of exposed animals, although one animal did have a well-differentiated pulmonary adenocarcinoma. The authors observed that this tumor's relatively short latency period and the low spontaneous incidence (0.1%) of such tumors suggested that it resulted from cadmium exposure.

Both the Sander and Mahaffey (1984) study and the Hadley et al. (1979) study are not adequate to assess carcinogenic potency, since the animals were only exposed for short periods and, in the Hadley et al. (1979) study, were not followed for sufficient time. Without continuous exposure, effects in the lungs may not occur or the study may not be sensitive enough to detect adverse effects.

In the only long-term inhalation study, Takenaka et al. (1983) exposed rats to several concentration of a cadmium chloride aerosol. Groups of 40 male Wistar rats were exposed to a continuous (23.5 hours/day) airborne concentration of 13.4, 25.7, or 50.8 μg of cadmium/m^3 of air for 18 months. A control group of 41 rats was exposed to filtered room air. The aerodynamic mass median diameter of the aerosol particles was 0.55 μm with a arithmetic standard deviation of 0.48 μm and a geometric standard deviation of 1.8 μm. The rats were followed for an additional 13 months before surviving rats were sacrificed.

There were no statistically significant differences seen in body weight or survival between exposed and control groups. The incidence of lung carcinomas was significantly increased ($p > 0.014$, Fisher's Exact Test) in all exposure groups. Three lung tumor types were identified, adenocarcinoma, epidermoid carcinoma, and mucoepidermoid carcinoma. The numbers of animals in each group that had these tumors types are given in Table VII-4. The first lung tumor was observed at 20 months. In the high-dose group, the first tumors were observed at 23 months and 23 out of 25 animals in this group dying or sacrificed after 27 months had lung tumors. Thus, these appear to be late-developing tumors.

Table VII-4

Lung Tumors in Rats Exposed to
Cadmium Chloride Aerosols

Exposure Group[a]	No. of Rats Examined Histologically	No. of Rats with Tumors			
		Adenocarcinoma	Epidermoid Carcinoma	Mucoepidermoid Carcinoma	Total Carcinomas
Control	38	0	0	0	0
13.4μg/m^3	39	4	2	0	6
25.7μg/m^3	38	16	5	0	20[b]
50.8μg/m^3	35	15	8	3	25[b]

[a] Airborne exposure concentrations are based on the cadmium, not cadmium chloride, concentration.

[b] One rat had both an adenocarcinoma and an epidermoid carcinoma.

Source: Takenaka et al. 1983.

This observation suggests the need for studies of long duration in order to detect increased tumor incidence from exposure to other cadmium compounds.

Summary

Injection and inhalation exposures to cadmium have caused increases in the incidence of neoplasms. No study, in which cadmium has been administered by the oral route, has shown such exposure to induce neoplasms. The most likely explanations for this discrepancy are that limited gastrointestinal absorption reduces the systemically absorbed cadmium to levels that were too low for the statistical power of the studies to detect a carcinogenic response and the gastrointestinal tract epithelical tissue is not a sensitive tissue for cadmium induced carcinogenicity.

Human Studies

The EPA has produced a detailed and up-to-date review of the epidemiologic evidence on health effects due to cadmium exposure (EPA 1985). Staff members of DHS have summarized the most important and/or current studies in Table VII-5. Most of the studies were occupational mortality studies in which cause-specific death rates were compared to expected rates based on a standard population; the ratio of observed to expected yielding a standardized mortality ratio (SMR). The studies by Thun et al. (1985) and Varner et al. (1983) are both follow-up studies of the cohort examined by Lemen et al. (1976). The study by Armstrong

and Kazantzis (1983) combined men from 17 plants in which a potential for cadmium exposure is present. Two studies focused on prostate cancer incidence rather than mortality: a cohort study in an occupational setting (Sorahan and Waterhouse, 1985); and a case-control study from a population-based tumor registry (Ross et al. 1983). Inskip et al (1982) conducted an historical cohort SMR study on the populations of two towns, one with and the other without high soil cadmium content. A case-control study of renal cancer examined cadmium exposure via several routes (Kolonel 1976).

Outcomes examined in these investigations included cancer of the respiratory tract, prostate, bladder, kidney, and gastrointestinal tract; nonmalignant causes of death included: gastrointestinal disease, respiratory disease, nephritis and nephrosis; cerebrovascular disease, and hypertension. The results are not entirely consistent, but the evidence for an effect of cadmium exposure is strongest for lung cancer, prostate cancer, renal cancer, and nephritis and nephrosis. Discussions of carcinogenic effects are presented below in three sections:

(a) Genitourinary Cancer

(b) Respiratory Cancer: Overview

(c) Respiratory Cancer: Study by Thun et al.

Summary of Salient Epidemiologic Studies on Carcinogenicity of Inhaled Cadmium

AUTHOR & DATE	STUDY DESIGN	METHOD OF ANALYSIS	N	OUTCOMES	RESULTS	NOTES	HOW EXPOSURE ASSESSED
Lemen et al. 1976	Occup SMR Cohort consists of all workers exposed to cadmium and employed for > 2 years	SMR	292	All cancer Resp Ca Prostate Ca	+ + (+)	(+) significant only when analysis assumed a 20-year minimum latency period	No quantification
Thun et al. 1985	Occup SMR [followup of Lemen et al. but expanded cohort]	SMR	602	All cancer Resp Ca Prostate Ca Genito-urinary Ca Nonmalign GI dis Nonmalign resp dis	- + - - + -	Strong dose-response, unlikely to be due to confounders. Authors suggest nonfatal cases may be in excess, but no new deaths since study by Lemen et al.	Cumulative mg-days/m^3 using industrial hygiene surveys since 1943 and personal monitor measurements in 1973-1976.
Varner 1983	Occup PMR [followup of Lemen et al; expanded cohort differs from Thun by including nonwhites, nonmales, and guards and janitors]	PMR	585	All Ca Lung Ca Urinary organ Ca Bladder Ca Ulcer of stomach and duodenum Nonmalign resp dis	+ + + + + +	Dose response, potential for some confounding due to smoking $p < .01$ $p < .01$	Same as Thun et al. but in cumulative mg-years/m^3
Andersson et al. 1984	Occup SMR All men were also exposed to nickel, a recognized carcinogen.	SMR	525	All Cancer Nephritis and nephrosis Lung Ca Prostate Ca Bladder Ca Obstructive lung dis	- + - (-) (-) (-)	Significant in those with at least 15 years exposure Smoking habits among those alive in 1981 were similar to those of Sweden as a whole (-) "possibly" elevated though not statistically significant	Duration of employment. Authors acknowledge deficiency in this measure due to sharp decline in Cd levels over time.

Table VII-3 (cont.)

AUTHOR & DATE	STUDY DESIGN	METHOD OF ANALYSIS	N	OUTCOMES	RESULTS	NOTES	HOW EXPOSURE ASSESSED
Sorahan & Waterhouse 1983	Occup SMR	SMR	3025	All Ca	-		No quantification for SMR
				Prostate Ca	-		
	[followup of report by			Resp Ca	+		
	Kipling and Waterhouse 1967, not shown in this table]	RMLT	2912	Prostate Ca	(+)	No longer positive if initial cases of earlier study are excluded.	For RMLT Cumulative years of employment in (1) high or (2)high or moderate exposure job.
				Resp Ca	+	Positive for those with length of followup ≥ 30 years	
	Cohort consists of all potentially exposed workers.			Nonmalign resp dis	-		
Sorahan & Waterhouse 1985	Occup incidence [further followup of 1983 report by same authors]	SIR	2559	Prostate Ca incidence	(±)	Exclusion of 4 index cases yields nonsignificant result, while inclusion of the original 4 yields p = .001	No quantitative assessment All workers in factory were considered exposed if employed > 1 month.
						Cases based on Birmingham Regional Cancer Registry. Completeness of that registry's ascertainment was not discussed	
Armstrong & Kazantzis 1983	Occup SMR	SMR	6995	Prostate Ca	-		Each job was categorized as high, med, or low exposure. The workers were classified as "ever high," (3%) "ever medium," (17%) or "always low" (80%)
	Combined men from 17 major plants involved in processes using cadmium These workers were therefore exposed to different forms of cadmium, eg dusts, oxide fumes, etc. They were also heterogeneous with respect to other chemical exposures.			Lung Ca	(+)	SMR significant at p<.05 for workers with >10 years "always low" exposure. Other categories had low power.	
				Cerebrovascular dis	-		
				Hypertensive dis	-		
				Bronchitis	+	Highly significant for the small group with "ever high" exposure	

AUTHOR & DATE	STUDY DESIGN	METHOD OF ANALYSIS	N	OUTCOMES	RESULTS	NOTES	HOW EXPOSURE ASSESSED
Kolonel 1976	Case-control: 2 sets of controls -colon cancer -nonmalign digestive disease	Stratified RR	64 cases 72 colon cancer 197 non-cancer controls	Renal Ca	+	Disease group of noncancer controls was found by Thun et al. to have elevated mortality assoc with Cd exposure. This may strengthen the results. Renal cancer may be too rare to be detected in SMR studies.	Occ: high risk job in high risk industry(yes/no). Cd in tobacco: lifetime pack years - surrogate quantification. Cd in diet: dietary history used to establish unusually high Cd dietary intake.
Ross, Paganini-Hill & Henderson 1983	Case Control study of prostate cancer incidence	Matched pair OR, also PIR for prostate vs other cancer	110 pairs	Prostate Ca	(-)	p > .05, but OR = 2 for job exposure to Cd	Employment in an occupation with possible Cd exposure, occupational history from interview
Inskip, Beral & McDowall 1982	Historical cohort of two towns, Shipham with high soil Cd content; Hutton with none	SMR however a direct comparison of rates in the two towns was not performed	911 for both towns	Respiratory dis GI Ca Lung Ca Prostate Ca Genito-urinary dis (inc: nephritis & nephrosis) Hypertensive dis Cerebrovascular dis	- - - - (+) (-) +	SMR significant at p < .10 for males SMR not significant but RR > 2 when comparing Shipham to Hutton residents: males, females, or sexes combined SMR significant at p < .05 for females or both sexes.	1979 soil samples were used to assign GI tract exposure levels to 70% of Shipham residents; homegrown food was considered main source. Assumed those exposures applied in 1939.

Abbreviations: N = number in cohort, Cd = Cadmium
SMR= Standardized mortality ratio, PMR = Proportional mortality ratio, PIR = Proportional incidence ratio,
RMLT = Regression method of life tables, SIR = Standardized incidence ratio, RR = Relative risk, OR = Odds ratio
+ indicates a statistically significant positive association with $p \leq .05$

Genitourinary Cancer

Noncarcinogenic effects of cadmium on kidney function have been well documentd (See Section VII.H), however, the rarity of renal cancer renders prospective studies impractical for detecting an increase in neoplasms at this site. A case-control study of renal cancer among an occupationally exposed population utilized two control groups: (i) colon cancer cases (as a means of equalizing proclivity for recall of previous exposure), and (ii) nonmalignant digestive disease cases (Kolonel 1976). The renal cancer cases were characterized by a greater odds of having worked in a job with a high risk of cadmium exposure than either control group. Later findings by Thun et al. 1985, Varner 1983 showed that nonmalignant digestive disease may also be associated with cadmium exposure. Since any association between the disease of the control group and cadmium will tend to mask the effect on renal cancer, the positive finding by Kolonel is more convincing. In addition, a review of death certificates by Andersson et al. (1984) disclosed a case of renal cancer, which the authors believed was due to 30 years of cadmium exposure. Staff members of DHS conclude that the evidence is insufficient to infer causation, but is suggestive of an association between cadmium exposure and renal cancer.

The case for an association with prostatic cancer remains inconclusive. Table VII-6 summarizes the epidemiologic evidence for such an association. Lemen et al. (1976) found an excess of prostate cancer deaths among 292 workers employed for greater than two years in a job

with potential cadmium exposure. The excess was significant if the analysis assumed a 20-year latency period. However, a follow-up study of this cohort by Thun et al. (1985) uncovered no new deaths due to prostatic cancer. The authors suggested that given the generally nonfatal nature of the disease, mortality studies frequently may not be sensitive enough to detect a potentially real association with incidence of prostate cancer. Sorahan and Waterhouse (1983, 1985) followed up a 1967 report by Kipling and Waterhouse which had found a highly significant excess incidence of prostatic cancer. Both the incidence report (Sorahan & Waterhouse, 1985) and the mortality study (Sorahan & Waterhouse, 1983) found no significantly elevated risk if the original four index cases were excluded. However, inclusion of these cases in the analysis yielded a highly significant association. For mortality, using cumulative years of high exposure to cadmium, the p-value was less than .05 when controlling for sex, year of study, employment, age at starting employment, and duration of employment. For morbidity, using more than one year of high exposure, $p<0.001$ (1.99 expected, 8 observed, p-value not given by authors but calculated by DHS staff based on a Poisson distribution). Tumor incidence was determined using the Birmingham Regional Cancer Registry. The authors do not provide information on completeness of ascertainment by this registry.

The SMR study by Andersson et al. (1984) and the matched case-control study by Ross et al. (1983) both failed to reject the null hypothesis of no effect on risk of prostate cancer. However, the SMR was considered "possibly" increased and the lack of statistical

Table VII-6

Association Between Cadmium Exposure
and Prostate Cancer Deaths

Authors	Magnitude of Association	Significant at p<.05
Sorahan & Waterhouse 1983	SMR=121 excluding 4 index cases	N[a]
Armstrong & Kazantzis 1983	SMR=99 for entire cohort	N
Andersson et al. 1984	SMR=129 for entire cohort =188 for those with >15 years exposure	N
Inskip et al. 1982	SMR=121	N
Lemen et al. 1976	SMR=348 for all workers =452 for those with >20 years followup	N Y
Ross et al. 1983	OR=2.0	N
Thun et al. 1985	SMR=213 for those with >20 years followup and >2 years exposure	N
Varner 1984	PMR=169	N

[a] Y if 4 index cases are included

significance could have been due to deficiencies in the measure of exposure. Similarly in the study by Ross et al., the odds ratio (OR) for cadmium exposure among prostatic cancer cases as compared to controls was 2. The smallest OR which would have an 80% chance of being detected as statistically significant in a study this size is 4, thus the lack of significance should be interpreted cautiously.

Calculations of the statistical power for detecting relative risks of 1.25, 1.5 and 2.0 for "negative" studies of prostate (and respiratory) cancer mortality are shown in Table VII-7. It is clear that, in general, the power of these studies was not sufficient to detect the small relative risks for prostate cancer deaths expected from cadmium exposure.

The evidence appears to be inconclusive regarding the effect of cadmium exposure on prostatic cancer. Given the highly significant early reports, it may be that cadmium acts as a promoting agent, inducing earlier tumors in those already susceptible. This effect may have been reduced markedly in recent years due to the lowering of exposure levels, sometimes by an order of magnitude or more (Thun et al. 1985, Andersson et al. 1984, Sorahan and Waterhouse 1985). Thus, those with earlier exposure may have been at highest risk, and the cohorts most recently studied, being heterogeneous with respect to their exposures, show only nonsignificant increases in prostate cancer incidence, e.g., a doubling or less, and no increase in mortality.

Table VII-7

Power to Detect an Elevated SMR at $\alpha = 0.05$

	If true SMR is:		
	125	150	200
1. Prostate Cancer			
Thun et al. 1985	0.06	0.12	0.28
Andersson et al. 1984	0.10	0.19	0.43
Sorahan & Waterhouse 1983	0.13	0.29	0.67
Inskip et al. 1982	0.04	0.08	0.21
2. Respiratory Cancer			
Andersson et al. 1984	0.10	0.22	0.54

Because the human studies repeatedly find some elevation in risk, albeit a nonsignificant one, the staff of DHS does not believe that the is evidence is conclusive to reject an effect of cadmium on prostate cancer.

The PMR analysis by Varner (1983) showed the proportion of bladder cancer deaths to be in excess of what would be expected in the standard US population. The occupational SMR study by Andersson et al. (1984) showed a nonsignificantly elevated risk of bladder cancer deaths. The data are too scant to be conclusive regarding the effect of cadmium exposure on bladder cancer.

Respiratory Cancer: Overview

Table VII-8 summarizes the epidemiologic evidence relating respiratory cancer SMR's to cadmium exposure. A significantly increased risk of respiratory cancer deaths was seen by Lemen et al. (1976), Thun et al. (1985), Sorahan and Waterhouse (1983), Varner (1983), and Armstrong and Kazantzis (1983), but not by Inskip et al. (1982) nor by Andersson et al. (1984). However, the assessment of exposure in the two towns investigated by Inskip et al. relied only on 1979 soil samples for exposure from 1939 to 1979. Even with a questionable exposure assessment, males in the exposed town had a lung cancer SMR which, while not statistically significant, was nearly double that of males in the unexposed town (101 vs 55). The other negative study (Andersson et

Table VII-8

Association Between Cadmium Exposure
and Respiratory Cancer Mortality

Authors	SMR	Significant at p<.05
Sorahan & Waterhouse 1983	127	Y
Lemen et al. 1976	235	Y
Thun et al. 1985	229	Y
Armstrong & Kazantzis 1983	126[a]	Y
Inskip et al. 1982	101[b]	N
Andersson et al. 1984	120	N

[a] For workers with >10 years exposure in the "always low" category (the number of workers with "ever medium" and "ever high" exposures was small).

[b] vs. SMR=55 for the unexposed town.

al.) had low statistical power to detect a SMR of less than 200 (see Table VII-7). In other studies, the range of SMR's for respiratory cancer was 120-230 (see Table VII-8). The staff of DHS concluded thatthe two negative studies for respiratory cancer are not convincing evidence of no effect, due to low statistical power in one study and poor exposure data in the other.

The study by Thun et al. (1985) showed a positive dose-response relationship where dose was expressed as cumulative mg-days/m^3. Varner (1983) reported the lung cancer PMR (proportional mortality ratio) to be elevated (see Table VII-5 for description of how this cohort differs from that of Thun et al.). Sorahan and Waterhouse (1983), in two separate analyses, found an elevated risk of respiratory cancer. The first analysis was based on the SMR and included all potentially exposed workers. The second analysis used the regression method of life tables (RMLT) and assessed exposure by cumulative years employed in a (1) high exposure job or (2) high or moderate exposure job or (3) high or moderate exposure job excluding welding. Measures (2) and (3) resulted in a significant effect of exposure on respiratory cancer, particularly for those with more than 30 years of follow-up.

In epidemiologic studies, the potential for confounding due to extraneous risk factors requires attention. If a cadmium-exposed cohort smoked excessively, or experienced exposures to other carcinogens, such as nickel or arsenic, then the apparent association between cadmium and respiratory cancer, for instance, could be at least partially explained by these factors.

Heavier smoking among cadmium workers as compared to the general population could account for the small but statistically significant SMR for lung cancer (126) observed by Armstrong and Kazantzis for those exposed >10 years at the "always low" catagory. No smoking histories were available. Sorahan and Waterhouse also lacked data on smoking, but they argue that smoking was unlikely to have been a confounder for two reasons. First, their analysis showed an increasing association with duration of employment, while smoking habits are unlikely to be well-correlated with duration of employment. Secondly, deaths from other diseases of the respiratory system were not elevated, as they would have been if the cohort had included a disproportionate number of smokers. However, the effect of nickel hydroxide could not be disentangled from that of cadmium oxide in this cohort.

The strongest evidence for cadmium-induced carcinogenicity in humans is the study conducted by Thun et al. The characteristics of this study which make it particularly convincing are the quality of the exposure data and the analysis of potential confounding. Since the quantitative results of this study constituted the basis for the DHS risk assessment of cadmium, a full description of this study is presented below.

While some of the observed association between lung cancer and cadmium may be explained by confounding factors, the consistency of results for several cohorts and several types of analyses, the dose-response pattern seen in the one study with quantitative exposure data, the finding in some studies that other smoking-related causes of death were not

elevated, and the magnitude of effect observed, suggest that confounding cannot explain all of the association.

The evidence from epidemiology strongly supports the hypothesis that cadmium exposure is associated with an increased risk of respiratory cancer. Since this site has also been implicated in animal bioassays of carcinogenicity, DHS staff members concluded that there is a high probability that the observed association is not spurious and that an inference of causality is justified.

Respiratory Cancer : Study by Thun et al.

Thun et al. conducted a follow-up of the report by Lemen et al. (1976), who had found an increase in mortality from respiratory and prostate cancer and from nonmalignant lung disease in a cohort of cadmium smelter workers. Thun et al. expanded the cohort and extended the follow-up period. The final cohort included those hired after 1925 and employed 6 months or longer in production areas of the plant during the period 1940-1969. The cause-specific death rates were adjusted by the indirect method to yield standardized mortality ratios (SMRs) and by the direct method to yield standardized rate ratios (SRRs). The SMR for lung cancer in the overall cohort was 147, while for those with 2 or more years of employment it was 229, with a 95% confidence interval of (131,371).

Exposure data that had been collected since the 1940's allowed evaluation of the lung cancer SMR by dose. Industrial hygiene measurements for departments and job sites with potential cadmium exposure were available (Smith et al. 1980). These were combined with individual work histories for each member of the cohort in order to assign an exposure level to each work day. Interruptions of employment were taken into account and exposure levels were adjusted to reflect respirator usage in departments where these were worn. A cumulative exposure in mg-years/m^3 was then assigned to each person-year of follow-up for each worker. The range of cumulative exposures was divided into three categories, and both SMRs and SRRs were calculated for each category. The results are shown in Table VII-9 using US white males as the comparison population, and in Table VII-10 using Colorado white males as the comparison population. (Thun presented the analysis using Colorado white males as the control group at the Fifth International Cadmium Conference February 1986, in San Francisco. This analysis assumes that pre-1950 lung cancer rates equaled those in 1950, since cause-specific rates were not tabulated in that state before 1950.)

The data indicate a clear dose-response relationship between cumulative cadmium exposure and the risk of death due to lung cancer. Using the US population as the comparison group, both the SMR and the SRR rise from about 1/2 the expected at "low" cumulative exposure to about 3 times the expected at high cumulative exposure. Both of these measures of risk are larger when the Colorado population is used as a standard, with the SRR rising from 0.7 to over 5.0.

The strength of evidence of causality provided by any single study depends on the degree to which one can rule out alternative explanations of the observed effect. Alternative explanations fall into 3 categories. (1) chance, (2) bias, (3) confounding. The study by Thun et al. is examined below in this context.

Chance

Thun et al. calculated the standardized rate ratio (SRR) for each of 3 exposure groups. (The person-years at risk, rather than individual workers, were classified by cumulative exposure to that point in time.) The SRR is suitable for subgroup comparisons, but not for external comparisons. A regression of the SRRs yielded a slope of 7.33×10^{-7}, which differed from zero with a probability of .0001. In other words, the probability that the increase in lung cancer risk associated with increasing exposure to cadmium was due to chance was about one in ten thousand.

Bias

Selection criteria described by Thun et al. appear to have been unbiased: all retired, deceased, and active employees who had worked a minimum of 6 months in production areas of the plant were included in the cohort. In calculating cumulative exposure, dates of interruption of employment were accounted for. Since more than 80% of the workers were followed for 20 or more years it is likely that the follow-up was sufficient for many latent cadmium-induced cancers to become manifest

and lead to death. Trained nosologists evaluated the death certificates. As indicated by Thun et al., one lung cancer death was originally miscoded as being due to another cause. Removal of this death from the lung cancer deaths (i.e. restoring it to the original, but incorrect coding) is necessary in order that the comparison with general population rates be unbiased (since miscodings also occur in the general population). However, the findings are not altered in any substantial way by this reclassification.

Exposure categories were chosen prior to the analysis. The cumulative exposure for all person-years was miscalculated by Thun et al. because they included non-workdays. This does not cause bias for purposes of inference since the misclassification was equivalent for all exposure categories. It would, however, alter the dose-response relationship, and therefore DHS staff adjusted for this error in conducting our risk assessment, since an overestimate of exposure would result in an underestimation of potency. The corrected exposures are shown in Tables VII-9 and VII-10. (See also Table IX-3.)

Confounding

If the cadmium-exposed workers included a disproportionate number of individuals with exposures to other agents responsible for lung cancer, then the observed association might be spurious. The potential confounders with regard to lung cancer mortality in this cohort were smoking and arsenic exposure.

(a) Smoking:

Indirect evidence that smoking was not a confounder in this cohort is provided by the cardiovascular death rate in this cohort, which was 35% lower than expected based on U.S. white male death rates. If this cohort included a higher proportion of total smokers or heavy smokers as compared to the general population of white males in the same age categories, then one would expect an increase (or at least not a deficit) in the cardiovascular death rate as well.

Data on the smoking habits of these workers were provided to Thun et al. by the company. The data came from company medical records and from a questionnaire survey mailed to surviving workers or the next-of-kin in 1982. The results of this survey have elicited differing interpretations depending on the choice of measure of smoking and on the choice of the comparison group. The 1985 paper by Thun et al. reported data on 70% of the workers. For these workers, the data indicated that as of 1982, 77.5% were current or former smokers compared to 72.9% current or former smokers among U.S. white males 20 years or older reported in the 1965 Health Interview Survey (HIS) conducted by the National Center for Health Statistics. It is clear that these 2 figures are not comparable since data from 1982 for the exposed group were compared with data from 1965 for the control group.

In the updated report by Thun et al. (1986), presented at the Fifth International Cadmium Conference in San Francisco, February 6, 1986, the authors provide a more meaningful comparison by limiting the

Table VII-9*

LUNG CANCER (ICD 162-163) MORTALITY BY CUMULATIVE EXPOSURE
WHITE MALE CADMIUM WORKERS HIRED ON OR AFTER 1/1/26
COMPARED TO U.S. DEATH RATES

EXPOSURE (cumulative mg/m^3) RANGE	MEDIAN	PERSON YEARS AT RISK	DEATHS	SMR	SRR
≤384	184.1	7005	2	53	.48
385-1920	795.6	5825	7(6)†	152(130)†	1.55(1.33)†
≥1921	2761.6	2214	7	280	3.45
		U.S. WHITE MALES		100	1.00

* Adapted from Thun et al. 1986, Table 7.
† Numbers in parentheses exclude one lung cancer death which was originally miscoded as being due to another cause.

Table VII-10*

LUNG CANCER (ICD 162-163) MORTALITY BY CUMULATIVE EXPOSURE
WHITE MALE CADMIUM WORKERS HIRED ON OR AFTER 1/1/26
COMPARED TO COLORADO DEATH RATES, 1950-79

Cumulative Exposure ($mg\text{-}days/m^3$)	PERSON YEARS AT RISK	DEATHS	SMR	SRR
≤384	7005	2	76	.70
385-1920	5825	7(6)†	212(182)†	2.29(1.96)†
≥1921	2214	7	387	5.09
COLORADO WHITE MALES			100	1.00

* Adapted from Thun et al. 1986, Table 8.
† Numbers in parentheses exclude one lung cancer death which was originally miscoded as being due to another cause.

Table VII-11

SMOKING HABITS OF
CADMIUM-EXPOSED COHORT

	1982 Survey Cadmium-Exposed Cohort	1970 HIS Sample[1]		
		Total	Operators & Kinded	Craftsmen & Foremen
Average age	61.5	44	39	42
% ever smoked	77.5[2]	76	79	83
% smoked a pack or more a day (includes current and former smokers)	10.8*[3]	44	49	53
Average length of smoking	--	23	20	22
% with > 20 cumulative pack years	53[2]	--	--	--

* This represented 25 or more cigarettes per day rather than 20 or more.

1 Health Interview Survey, conducted by National Center for Health Statistics, reported in Sterling and Weinkam 1976.

2 Varner 1983, based on 35% of workers.

3 Thun et al. 1986, based on 49% of workers.

smoking analysis to the 49% of the cohort for whom lifetime smoking histories were available. These data indicated that as of 1965 a larger percentage of the cadmium-exposed cohort were nonsmokers and a smaller percentage were heavy smokers compared to general population rates available from the HIS. The year 1965 was chosen since this was the midpoint of the study.

A different view of these data was presented by Varner (1984) who examined cumulative pack-years smoked by members of the cohort. He sugested that this cohort had far more heavy smokers than blue collar workers reported in the 1970 HIS, and that "smoking prevalence tends to be highest among blue collar workers." However, in the HIS survey the average age of the white males was 39 (operatives and kindred), 42 (craftsmen and foremen) and 44 (total sample). In the cadmium-exposed cohort the average age was no less than 53, and was estimated as 61.5. It is therefore surprising how similar some of the smoking characteristics of these populations are (see Table VII-11).

The percent who "ever smoked" was 77.5% in the cadmium-exposed cohort, and 76% in the total HIS sample. The data on the cadmium workers represented information from only 36% of the cohort. Given that the cohort under study was considerably older than the HIS sample, that the HIS survey was done about 10 years earlier than the survey of the cadmium cohort, and that different information was reported from these two surveys, the differences between the smoking habits of the total

HIS sample and those of the cadmium-exposed workers do not appear to be very large.

The magnitude of confounding from differential smoking habits can be assessed. A method to estimate the contribution of smoking to lung cancer mortality in the cohort is described by Axelson (1978). The method is applied to the lifetime smoking histories summarized by Thun et al. The calculations (summarized in Table VII-12) are based on information regarding smoking habits in the exposed group, smoking habits in the comparison group, and the relative risk for lung cancer at each level of smoking. In view of the data indicating a deficit of smokers in this cohort compared to the general population, the baseline SMR for lung cancer would have been reduced 30%.

It is unknown, however, whether the smoking histories of the 49% sample were representative of the cohort as a whole, and whether the histories themselves were biased, since they were collected retrospectively. While smoking may have confounded the relationship between cadmium and lung cancer, it is unlikely that smoking was responsible for all of the excess. Furthermore, if the smoking habits in this cohort were correctly reported, i.e., if the observed deficit of smokers was real, then the excess of lung cancer deaths is larger than originally

Table VII-12*

TECHNIQUE USED TO ADJUST FOR CIGARETTE SMOKING

	Percent of Population, 1965				
	Nonsmokers (1x)[3]	Moderate[1] Smokers (10x)	Heavy[2] Smokers (20x)	Rate Ratio of Overall Population Relative To Nonsmokers	Rate Ratio Relative To U.S.
POPULATION					
Exposed[4]	48.4%	40.8%	10.8%	6.724	0.70
U.S.	27.1%	53.0%	20%	9.571	1.00

* Thun et al., 1986

[1] 1-24 Cigarettes/day

[2] 25+ Cigarettes/day

[3] The numbers in parentheses refer to the relative risk for lung cancer associated with each level of smoking.

[4] Usable information available on 250 persons hired after 1926.

calculated. In other words, confounding due to smoking did not create the appearance of a nonexistent carcinogenic effect from cadmium; rather, the confounding reduced the apparent magnitude of cadmium's carcinogenicity.

(b) Arsenic

The plant employing the workers in this cohort refined cadmium metals and compounds from 1926 onwards. Between 1918 and 1925 it had functioned as an arsenic smelter. Therefore, the analysis by Thun et al. excluded workers employed prior to January 1, 1926. (For those employed prior to 1926 the lung cancer SMR was 714). Nevertheless it is possible that residues of arsenic contributed to the lung cancer excess for those first employed in 1926 or later.

To estimate the possible contribution of arsenic to lung cancer in this cohort, Thun et al.:

(1) identified the departments and job categories which were likely to have involved continued exposure to arsenic;

(2) calculated the proportion of person-years spent in areas with probable arsenic exposure based on personnel records (20%);

(3) evaluated industrial hygiene measurements to estimate air concentrations (range = 300 to 700 $\mu g/m^3$, Thun used midpoint = 500 $\mu g/m^3$);

(4) estimated the total years of employment for workers in the cohort (1728 years);

(5) based on (2),(3), and (4), estimated that total arsenic exposure amounted to 345.6 person-years of exposure to air levels of 500 $\mu g/m^3$;

(6) assumed a 75% respirator protection factor (i.e. inhaled exposures were 25% of air concentrations or 125 $\mu g/m^3$). This yielded a total exposure of 43,200 μg-years/m^3.

Using a risk assessment model developed by OSHA for arsenic carcinogenicity, Thun calculated that 43,200 $\mu g/m^3$ years of exposure to arsenic would contribute no more than .768 lung cancer deaths.

This may represent an overestimate of the contribution of the arsenic exposure to the lung cancer excess. The reasons submitted by Thun are as follows:

1) Only a fraction of jobs in the "arsenic areas" had exposures as high as the furnace area (500 $\mu g/m^3$)
2) The high exposure jobs were frequently staffed with brief employment-entry (sic) level workers who are not in the study cohort
3) Urinary arsenic levels on workers in the "high arsenic" areas from 1960-80 averaged only 46 $\mu g/l$ (equaling an inhaled arsenic of 14 $\mu g/m^3$)
4) Thus, assuming an average inhaled arsenic concentration of 125 $\mu g/m^3$ for these years overestimates the dose by .9 fold
5) ASARCO has previously argued that the OSHA risk assessment overestimates "by a factor of three or more" the expected increase in mortality from respiratory cancer.

(Thun, personal communication)

On the other side of this argument, the estimates of dose may not be reliable. The presumed relationship between urinary arsenic and inhaled arsenic may be incorrect, and is currently being reanalyzed (personal communication, Dr. Philip Enterline). Urinary measurements before 1960 were not available, and the earlier exposures would be expected to be greater. Furthermore, the figure of 125 $\mu g/m^3$ could be an underestimate since the respirator protection factor is based on a 1976 survey which compared air samples and personal samples. It is well known that earlier respirators were less effective, and in many cases compliance in earlier years was lower.

It is unclear, therefore, what the contribution of arsenic may have been to the overall excess of lung cancer deaths in the cadmium-exposed cohort studied by Thun et al. If the OSHA risk assessment model is correct, then under the assumption of no protection from respirators, the maximum number of excess lung cancer deaths attributable to arsenic would be 3.07 for the whole cohort. The excess attributable to arsenic is compared to the observed excess lung cancer deaths in Table VII-13 (unadjusted for smoking) and in Table VII-14 (adjusted for smoking). The adjustment for smoking is based on the analysis of smoking histories and assumes that smoking is independent of arsenic exposure within the plant, and that there is no interaction between these two exposures. The actual excess was 5.13 (unadjusted for smoking) or 8.39 (adjusted for smoking) if the whole cohort is considered; the excess was 9.00 (unadjusted for smoking) or 11.10 (adjusted for smoking) if only those with 2 or more years of exposure are included.

The last issue with respect to confounding concerns the combined effects of arsenic and smoking on lung cancer, which are more than additive, though probably less than multiplicative. Therefore, if any of the workers who were exposed to arsenic were smokers, there could also be confounding from the interactive effect of these two exposures. However, when relative risks are small (e.g., less than 1.3), there is very little difference between additive and multiplicative effects. Since it is unlikely that in this cohort the relative risk associated with either arsenic or smoking is larger than 1.3, the effect of any interaction is likely to be negligible. (If both relative risks are 1.3, multiplying yields 1.69, adding yields 1.6, difference = .09.)

In conclusion, given the low level of arsenic exposure and the evidence indicating a deficit of smokers in this cohort, DHS staff believes that the apparent association between cadmium exposure and lung cancer is not likely to be explained by confounding from smoking and/or arsenic exposure.

Finally, to summarize the DHS staff's findings with regard to the study by Thun et al.: the SMR of 2.3 in those with more than 2 years of cadmium exposure and the dose-response relationship are unlikely to be explained by chance, by bias, or by confounding from smoking and/or arsenic exposure. The staff of DHS concludes that the excess of lung

Table VII-13

THE POSSIBLE CONTRIBUTION OF ARSENIC TO THE EXCESS IN LUNG CANCER DEATHS

Observed	Expected[1]	Excess	Number Attributable To Arsenic
16	10.87	5.13	.768-3.07
16	7.00	9.00	---[2]

[1] Based on age- and calendar-year-specific lung cancer death rates for white males in the U.S. The first line refers to the whole cohort. The second line refers to workers with a minimum of two years employment (Thun et al. 1985).

[2] Not calculated but is certainly less than for the whole cohort.

Table VII-14

THE POSSIBLE CONTRIBUTION OF ARSENIC TO THE EXCESS IN LUNG CANCER DEATHS AFTER ADJUSTMENT FOR SMOKING[1]

Observed	Expected[2]	Excess	Number Attributable To Arsenic
16	7.61	8.39	.768-3.07
16	4.90	11.10	---[3]

[1] Assumes underlying SMR of .70 as shown in table VII-11, and no interaction.

[2] Based on age- and calendar-year-specific lung cancer death rates for white males in the U.S. The first line refers to the whole cohort. The second line refers to workers with a minimum of two years employment (Thun et al. 1985).

[3] Not calculated but is certainly less than for the whole cohort.

cancer deaths in the study by Thun et al. is best explained by exposure to high levels of cadmium. The DHS staff further concludes that while other confirmatory studies are desirable this study constitutes strong evidence of human carcinogenicity.

3. Mechanism

The biochemical mechanism(s) behind cadmium-induced mutagenic and carcinogenic effects is (are) not known. A number of possible mechanisms were discussed by Sunderman (1984). There is evidence that cadmium may act as an indirect mutagen or carcinogen but there are also substantial data indicating cadmium can directly interact with DNA and can therefore be a direct acting mutagen or carcinogen.

Cadmium can inhibit the activity of several individual enzyme activities and enzyme systems in vivo and in vitro. These include mitochondrial oxidative phosphorylation (Kamata et al. 1976), fidelity of DNA synthesis (Sirover and Loeb 1976), RNA synthesis (Stoll et al. 1974), protein synthesis (Norton and Kench 1977), and hepatic mixed function oxidase enzyme activities (Teare et al. 1977; Furst and Mogannam 1975). The effect on some enzyme activities may be the result of displacement by cadmium of the metal ion, such as zinc, in a metalloenzymes. If cadmium inhibits or alters enzyme activities involved in DNA replication or repair, somatic mutations may result. Cadmium

may also act as a cocarcinogen by altering the metabolism of a procarcinogen (Jennette 1981).

Cadmium has also been found to directly bind to isolated DNA at specific high affinity sites (Waalkes and Poirier 1984) and to cause mispairing in complexes formed between synthetic polynucleotides (Murray and Flessel 1976). Other metals, such as zinc, magnesium, and calcium, can antagonize the binding of cadmium to isolated DNA, but cadmium was found to have the highest affinity for the binding sites (Waalkes and Poirer 1984). In an in vivo study (Hidalgo and Bryan 1977), labeled cadmium was found to localize in the nucleus of liver cells. It was found to be concentrated more in nonhistone than histone proteins.

The direct interaction of cadmium with DNA and the number of positive mutagenic and clastogenic studies suggest that cadmium may have a direct effect on DNA. The interaction between cadmium and other metals found by Waalkes and Poirer (1984) may explain the inhibitory effect of these metals on cadmium-induced carcinogenicity.

4. Conclusion

The staff of the Department of Health Services (DHS) agrees with the International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA) that there is sufficient evidence to conclude that cadmium is an animal carcinogen. The DHS staff's

conclusion is based in part on the findings of distant site tumors, interstitial cell tumors of the testis, following subcutaneous administration of cadmium salts to two species, rats and mice (Gunn et al. 1983, 1964; Levy et al. 1973). EPA (1985) presents a good review of literature supporting the use of distant site tumors as evidence for the carcinogenic potential of a compound following subcutaneous injection. Although injection site tumors have also occurred, these are not considered sufficient evidence of a compound's carcinogenic potential. IARC (1982) also used the evidence of distant site tumors as the basis for their conclusion. Additional supporting evidence, not available at the time of the IARC decision, includes the studies of Poirier et al. (1983) and Takenaka et al. (1983). Poirier et al. (1983) found a significant increase in distant site tumors of the pancreas and the testis in rats given subcutaneous injections of cadmium chloride. Takenaka et al. (1983) observed a significant increase in lung tumors in rats exposed to a cadmium chloride aerosol. Both of these findings were also used as a basis for the DHS staff's conclusion.

The IARC last evaluated cadmium for carcinogenicity before the results of the study by Thun et al. were available. The EPA most recently evaluated cadmium in 1985 and concluded "there is limited epidemiologic evidence that inhaled cadmium is dose-related to lung cancer in exposed workers" (EPA 1985). The DHS staff considers all animal carcinogens to be potential human carcinogens. The DHS staff finds that the epidemiologic evidence supports an inference of a causal association between cadmium and respiratory cancer for the following reasons: (1)

the negative studies (Inskip et al. 1982, Anderson et al. 1984) had low statistical power and/or poor exposure data, (2) positive findings were present in several studies utilizing different cohorts and different types of analyses (Thun et al. 1985, Sorahan and Waterhouse 1983, Armstrong and Kazantzis 1983), (3) some of these studies found that other smoking-related causes of death were not elevated (Sorahan and Waterhouse 1983, Thun et al. 1985), (4) the single study with detailed quantitative exposure data showed a highly significant dose-response (Thun et al. 1985), (5) there were no sources of bias which could explain this finding, and (6) the same study, in examining confounding, found a potential deficit of smokers among the exposed workers, and estimated only a small contribution from arsenic, indicating that the positive finding was unlikely to be explained by these confounders.

The DHS staff concludes that while more confirmatory studies would be desirable before judging the sufficiency of the evidence, there is a high probability that cadmium is carcinogenic in humans.

VIII. Threshold Discussion

The noncarcinogenic effects of cadmium are believed to occur through mechanisms that have threshold exposure levels at and below which no effect will occur. The carcinogenic activity of cadmium may occur through a mechanism for which no threshold exposure level exists. Such a mechanism would probably involve direct interaction of cadmium with nuclear DNA. Biochemical studies have shown that there are high affinity binding sites for cadmium on isolated DNA and that cadmium can cause mispairing of synthetic polynucleotides (Walker and Poirier 1984; Murray and Flessel 1976). As described further in Section VII.J.1, there is suggestive but inconclusive evidence that cadmium is genotoxic.

There are mechanisms proposed by which compounds may induce a carcinogenic response without a direct effect on nuclear DNA. These mechanisms may have threshold exposure levels associated with them. Cadmium may also act by reducing the fidelity of DNA synthesis (Sirover and Loeb 1976). Cadmium may act as a cocarcinogen by altering the metabolism of a procarcinogen (Jennette 1981). Tissue injury, such as that observed in the testes, may also act as an indirect mechanism. However, these mechanisms are speculative: there is no compelling evidence that they are actually responsible for the observed carcinogenic response of cadmium.

In light of the above considerations, particularly the absence of compelling evidence of a threshold mediated mechanism, DHS staff concludes that cadmium's carcinogenicity should be treated as a nonthreshold phenomenon.

IX. Risk Assessment

Both carcinogenic and noncarcinogenic effects have been identified in the spectrum of cadmium-induced toxicity. Since there is a qualitative difference in how these processes occur, the hazards posed by these effects must be quantified in different ways. However, once the quantitative risks are determined, a judgement about the greatest potential hazard posed by a compound can usually be made. Below, the noncarcinogenic hazard posed by cadmium will first be quantified followed by a quantification of the carcinogenic hazard.

A. Noncarcinogenic Risk

Cadmium has been found to induce a number of noncarcinogenic toxic effects in experimental animals and humans. These effects include hypertension, endocrine changes, hepatotoxicity, osteomalacia and osteoporosis, anemia, immunosuppression, emphysema and pulmonary function changes, renal toxicity, fetotoxicity, and teratogenicity. Several of the effects have occurred in experimental animals at low exposure levels. Hypertension occurred in rats given drinking water containing as little as 0.1 ppm of cadmium over an 18-month period (Perry et al. 1977). This is an approximate intake of 5 μg/kg-day. Sporn et al. (1970) reported finding changes in liver enzyme activity in rats given drinking water containing 1 ppm (a dose of approximately 50 μg/kg-day). Effects suggesting immunosuppression occurred in mice receiving drinking water containing 3 ppm (a daily dose of approximately 500 μg/kg-day)(Koller et al. 1975, Exon et al. 1974).

Respiratory effects have been observed in experimental animals and humans at airborne concentrations of around 20 $\mu g/m^3$ but not at levels below 15 $\mu g/m^3$; these are equivalent to daily doses of approximately 6.0 and 4.5 $\mu g/kg$-day, respectively. Although these various effects have been reported to occur at relatively low levels of exposure, several authors and organizations have considered renal toxicity to be the most sensitive noncarcinogenic effect (Friberg et al. 1974, WHO 1977, and EPA 1981). Because the strongest and most abundant epidemiological evidence exists for this site, the staff of DHS has used renal toxicity as the basis for quantitative noncarcinogenic hazard assessments performed on cadmium.

As discussed in Section VII.H, Friberg et al. (1974) estimated that a retention rate of between 6.6 and 24.6 μg/day of cadmium would be necessary for the renal cortex concentration to reach 200 $\mu g/g$ wet weight over a 50-year period (see Table VII-1). Kjellstrøm et al. (1984) estimated that about 10 percent of a human population would show signs of renal toxicity at that concentration in the renal cortex. To achieve such a rate of cadmium retention from inhalation alone, Friberg et al. (1974) estimated that the ambient airborne concentration needed to be from 0.65 to 2.5 $\mu g/m^3$, assuming a 50 percent absorption of inhaled cadmium. The most likely concentration was estimated to be 1.5 $\mu g/m^3$, based on the assumption of a 19-year biological half-life for cadmium (see Section V.D).

The renal cortex concentration of 200 $\mu g/g$ wet weight tissue is not a threshold concentration but, at best, one that would produce an effect

in only 10 percent of a population. No threshold level has actually been determined, although renal toxicity is believed to have a threshold renal cortex concentration at which no toxicity will occur. An ambient air concentration of 1 ng/m^3 (0.001 μg/m^3) of cadmium is 650 to 2500 times less than the ambient air concentrations (0.65 to 2.5 μg/m^3), estimated by Friberg et al. (1974), that will lead to a renal cortex concentration of 200 μg/g wet weight following lifetime exposure. Although no threshold concentration for renal toxicity has been determined, staff members of DHS believe that the magnitude of the difference between exposure to lifetime ambient air cadmium concentrations at 1 ng/m^3 and at those concentrations that will induce renal toxicity in 10 percent of the population is sufficiently large so that there is little, if any, risk of renal toxicity from exposure to 1 ng/m^3 of cadmium. Exposure to an ambient air concentration of 10 ng/m^3 may pose a risk if the most conservative assumptions by Friberg et al. (1974) are correct. If the most likely assumption by Friberg et al. is correct, then exposure to an ambient air concentration of 10 ng/m^3 probably does not pose a risk of renal toxicity.

B. Carcinogenic Risk

Both experimental animal studies and epidemiological studies of worker population have indicated cadmium is carcinogenic. Quantitative assessments have been performed on both of these types of studies in order to obtain a range of risks. The quantitative risk assessment using the animal studies is discussed first, followed by a presentation

of the quantitative risk assessment based on the human epidemiological study.

1. Quantitative Cancer Risk Assessment Based on Animal Data

The animal study chosen as the basis for a quantitative risk assessment was that reported by Takenaka et al. (1983, see Appendix A). This is the only adequate long-term inhalation study and, as such, is the most relevant study to assess the carcinogenic potential of cadmium as an air pollutant. Several ingestion studies have been performed, but none showed a positive response. Injection studies have been positive for injection site tumors and tumors at remote sites. However, parenteral exposure is not normally considered an appropriate route for quantitative risk assessment.

Lung tumors were the only neoplasms found to be significantly increased in the study reported by Takenaka et al. (1983). The tumor incidences and exposure levels used for the low-dose extrapolation are given in Table IX-1. Assumptions used to determine these values are described below.

The tumor incidence data used in this analysis combines the three types of malignant lung tumors identified in the animal study. The separate incidence rates for each tumor type are given in Table VII-4. These tumor types were combined because they were all found in the sametissue and were all carcinomas. Two animals had one tumor identified

Table IX-1

Exposure Levels and Tumor Incidences
Used in Low Dose Extrapolation

Exposure Level[a] in $\mu g/m^3$	Incidence[b] (No. of animals with Tumors/ No. of animals examined)
0 (0)[c]	0/38
2.2(13.4)	6/39
4.1(25.7)	20/38
8.3(50.8)	25/35

[a] Human equivalent exposure values as cadmium, see text for explanation of how these values were determined.

[b] These included all malignant lung tumors. Lung tumor types identified were adenocarcinoma, epidermoid carcinoma, and mucoepidermoid carcinoma.

[c] Numbers in parentheses are average measured airborne cadmium concentrations during rat study.

Source: Takenaka et al. 1983.

as an adenocarcinoma and a second one identified as an epidermoidcarcinoma. These animals were only counted once in the incidence data.

The exposure levels used in the low-dose extrapolation calculations were human equivalent lifetime levels based on the animal exposure levels. Two assumptions were used to make these conversions. The first assumption was that the partial lifetime exposure of 18 months that the rats received could be made equivalent to a full lifetime exposure of 24 months by multiplying the average measured exposure

level by the ratio of the length of exposure to length of expected lifetime:

18 months/24 months = 0.75.

Since the animals were exposed for 23.5 hours per day, no conversion factor was used to make exposure equivalent to a 24 hours per day exposure expected for the human population in this assessment.

The second assumption was that the human equivalent ambient exposure concentrations could be calculated based on a body surface area scaling factor from the experimental exposure levels. However, a number of different scaling factors could have been used. Scaling factors take into account differences in body weight, surface area, metabolic rate, and/or lifetime. The staff of DHS has previously found that none of the commonly used scaling factors is empirically most appropriate for animal-to-human dose conversion in low-dose cancer risk extrapolation. Since several scaling factors appeared to give acceptable results, DHS staff members have decided to use surface area because it gives an intermediate measure of dose compared to other scaling factors and because surface area is related to metabolic rate, which may affect an organism's response to a carcinogen.

To use the surface area scaling factor, experimental exposure levels, in $\mu g/m^3$, are first converted to a daily dose, in $\mu g/kg\text{-}day$. Assumptions used for this conversion were that the rats inhaled 0.144

m^3/day and that 100 percent of the inhaled cadmium chloride aerosol is deposited in their lungs. (An absorption factor was not used because the tumors occurred at the site of contact and the importance of systemic absorption is not known for this effect.) Average group body weights provided by the authors, at 18 months into the study, were used for these conversions. These body weights were 0.425, 0.438, and 0.424 kg for exposure group levels 13.4, 25.7, and 50.8 $\mu g/m^3$, respectively. The calculation was performed as follows:

$$Ea(Va/Wa) = Da$$

where Ea is the experimental exposure level, which has already been transformed to a full lifetime exposure level; Va is the daily volume of air inhaled by a rat; Wa is the average group body weight; and Da is the daily dose level.

Conversion of the animal daily dose level Da to a human daily dose level based on surface area was done by a method used by EPA (1980b). This was accomplished by the following formula:

$$Dh = Da(Wa/Wh)^{1/3}$$

where Dh is the human equivalent daily dose and Wh is the assumed average human body weight, 60 kg.

Finally the human equivalent daily dose was converted to a human equivalent ambient air concentration by assuming an average daily human inhalation volume of 18.05 m^3/day.

$$Dh(Wh/Vh) = Eh$$

where Vh is the assumed human daily inhalation volume and Eh is the human equivalent exposure level.

A sample calculation for the experimental animal group exposed to 13.4 μg cadmium/m^3 is given below:

$$13.4\ \mu g/m^3 \times 0.75 = 10.05\ \mu g/m^3 = Ea$$

$$10.05\ \mu g/m^3 \times \frac{0.144\ m^3/day}{0.425\ kg} = 3.4\ \mu g/kg\text{-}day = Da$$

$$3.4\ \mu g/kg\text{-}day(0.425\ kg/60\ kg)^{1/3} = 0.65\ \mu g/kg\text{-}day = Dh$$

$$0.65\ \mu g/kg\text{-}day \times \frac{60\ kg}{18.05\ m^3/day} = 2.2\ \mu g/m^3 = Eh$$

Results of Low-Dose Extrapolation

Using the multi-stage extrapolation model (See Appendix B), the estimated excess human cancer risk from exposure to cadmium was

calculated based on lung tumor incidence in rats exposed to cadmium chloride aerosol, as reported by Takenaka et al. 1983).

The computer program, GLOBAL79, for low-dose extrapolation based on the multistage model, calculates the extra risk function by maximizing the likelihood function of the input data. The maximum likelihood estimate (MLE) and the 95% upper confidence limit (UCL) of excess risk can then be determined for any exposure level. The 95% UCL for extra risk is always linear at low doses, which is conceptually consistent with the linear nonthreshold theory of carcinogenesis. The slope of the 95% UCL, q*, is taken as a plausible upper bound of carcinogenic potency.

Because the animal exposure levels for cadmium were converted to human equivalent exposure, the 95% UCL, q*, is a measure of excess cancer risk for humans. If the lifetime daily exposure is expressed in ($\mu g/m^3$), then q* can be considered as the excess risk associated with this exposure. Since q* for humans is a measure of excess lifetime cancer risk associated with exposure to one unit (in $\mu g/m^3$) cadmium, it is termed the unit risk. The 95% UCL of excess risk may be approximated for any low level exposure to cadmium by the equation:

$$R = \text{unit risk} \times \text{dose},$$

where R is the 95% UCL of excess lifetime cancer risk. The unit risk for cadmium, based on the lung tumor incidence data, is 1.81×10^{-1} $(\mu g/m^3)^{-1}$.

Although the staff of DHS believes that the multistage model is the appropriate method to estimate low dose risk, other models have been used to show the range of risk estimates that can be obtained (See Appendix B). For comparison, the maximum likelihood estimate and 95% UCL of excess human lifetime cancer risk based on liver tumor incidence in male rats are presented in Table IX-2 for each model at two possible environmental exposure levels. The environmental ambient levels expected in California are believed to range around 0.001 to 0.003 $\mu g/m^3$ (1 to 3 ng/m^3, see Part A). The 95% UCL dose-response curve for each model can be seen in Figure IX-1. Usually, the multi-stage model is the most conservative model (finding the highest risk) at low dose levels. The probit is generally the least conservative model, followed in order by the gamma multi-hit, logit, and Weibull models. In this case, the multistage model is the most conservative, as expected, followed by the Weibull, gamma multi-hit, logit, and probit models.

Table IX-2

Maximum Likelihood Estimates and 95% Upper Confidence Limits for Excess Lifetime Cancer Risk from Exposures at 10^{-3} and 10^{-2} $\mu g/m^3$ Based on Different Low Dose Extrapolation Models[a]

	Ambient Air Concentration ($\mu g/m^3$)			
	10^{-2}		10^{-3}	
Model	MLE[b]	UCL[c]	MLE	UCL
Multistage	$1113/10^6$	$1807/10^6$	$111/10^6$	$181/10^6$
Probit	$< 1/10^6$	$< 1/10^6$	$< 1/10^6$	$< 1/10^6$
Logit	$13/10^6$	$68/10^6$	$< 1/10^6$	$1/10^6$
Weibull	$285/10^6$	$1140/10^6$	$16/10^6$	$79/10^6$
Gamma Multi-Hit	$42/10^6$	$145/10^6$	$1/10^6$	$4/10^6$

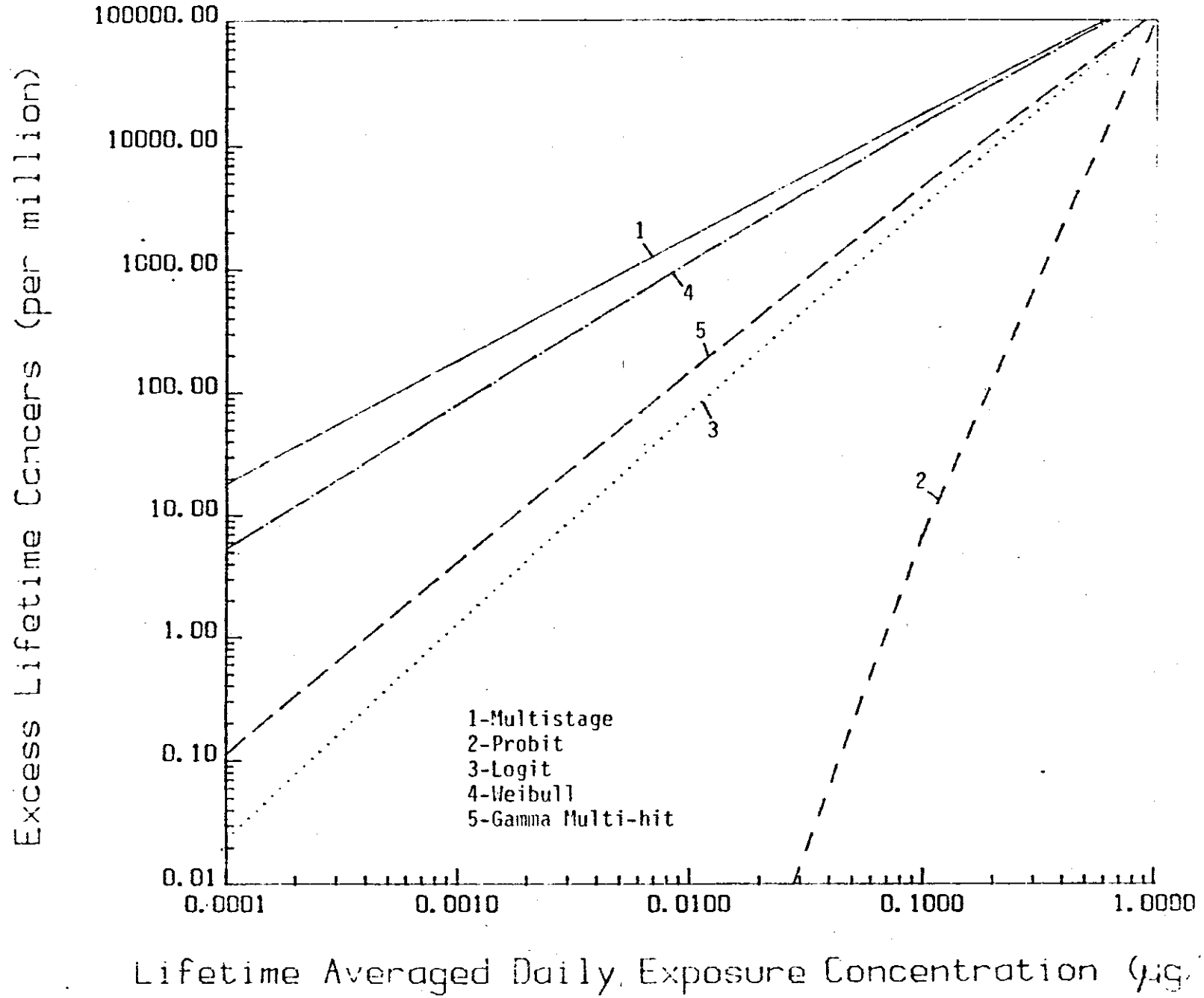
[a] Based on lung tumor incidence in male rats exposed to cadmium chloride aerosol, as reported by Takenaka et al. (1983)

[b] Maximum Likelihood Estimate, expressed as excess lifetime cancer cases per million population.

[c] 95% upper confidence limits, expressed as excess lifetime cancer cases per million population.

Figure IX-1

ESTIMATED HUMAN EXCESS LIFETIME CANCER RISK BASED ON MALE RAT LUNG TUMORS USING THE 95% UCL



2. Quantitative Cancer Risk Assessment Based on Human Data

Department of Health Services (DHS) staff conducted a quantitative cancer risk assessment for cadmium using the data from the occupational mortality study by Thun et al. (1985) and extrapolating to ambient levels in California. The strengths of this study are described elsewhere in this document (Section VII.J.2). The exposure data in this study were based on industrial hygiene measurements and individual work histories. These measurements consisted of historical area monitoring samples and, when appropriate, were adjusted to reflect respirator protection in departments where respirators had been worn. For workers employed 6 months or longer in production areas of the plant the person-years of follow-up were divided into 3 categories according to cumulative exposure in mg-days/m^3, (see Table IX-3). The risk of death from lung cancer for each exposure group was measured by the standardized mortality ratio (SMR). The data indicated a clear dose-response, with SMRs of 53, 152 and 280 for the low, moderate and high exposure groups. Because the study related quantified exposure levels to quantified measures of lung cancer risk, the data were suitable for a risk assessment.

DHS staff emphasizes that the risk estimates derived in conducting any risk assessment are not exact predictions, but rather represent best estimates based on current scientific knowledge and methods. It is important to recognize that uncertainties arise both in the data and in the extrapolation process, and that these uncertainties necessitate the use of assumptions. In its presentation of this risk assessment, the DHS staff has explained the assumptions made at each step, and the direction in which each assumption affected the risk estimates.

The choice of assumptions involves scientific judgment. Guided by our mandate to protect the public health, the DHS staff has chosen to use linear models for extrapolation purposes, because these models are likely to be health-conservative. With regard to assumptions about the data, the DHS staff has utilized the median exposure levels and maximum likelihood risk estimates. This approach leads to a plausible upper bound for risk estimates.

The carcinogenic risk assessment for cadmium is discussed in three sections which cover the following:

(1) the limitations of the data collected and reported by Thun et al.;

(2) the model which was fitted to the data, its mathematical representation, and the assumptions; and

(3) the application of the model to the general population to obtain a unit risk and upper confidence limit for this unit risk.

a. Limitations of the data used for quantitative risk assessment

Uncertainties stemming from the data on which the risk assessment was based fall into four main categories: (1) the accuracy of the exposure assessment for workers in the cohort, (2) the accuracy of the response or cancer mortality measurements, (3) the potential effects of confounding factors and (4) the application of the observed dose-response relationship to the California general population. A full discussion of potential confounding in this study is found in Section VII.J.2, Respiratory cancer - Thun study. The first three issues relate to internal validity in the measurement of a dose-response relationship among a group of cadmium-exposed workers; the fourth is an issue of external validity or generalizability beyond the study population.

(i) Uncertainties in the exposure estimates

Industrial hygiene area samples provided the basis for assessing exposure of individuals. For each job category, a quantitative exposure level was assigned. Each day of each worker's employment was classified into one of seven exposure-based job categories. While samples had been collected and measured beginning in the 1940's, the period of potential exposure for this cohort was 1926 - 1969 (inclusive). Two adjustments were made to these measurements: (1) conversion from area samples to personal exposure estimates was based on a 1973 - 1976 survey which compared area and personal samples; (2) adjustment of the personal exposure estimates to reflect respirator effectiveness was based on a 1976 survey of respirators.

Uncertainty as to the validity of the exposure estimates stems from (i) the application of 1940's measurements to earlier periods, (ii) the application of department-based data to individual workers, (iii) the use of a ratio determined in the 1970's for converting area samples to personal exposures for the entire exposure period, and (iv) the use of a respirator effectiveness factor determined in 1976 for the entire exposure period. The assumptions of (i) and (iv) are likely to result in underestimation of exposure, while the assumptions of (ii) or (iii) could be biased in either direction. The DHS staff knows of no way to quantify these uncertainties.

(ii) Uncertainties in the risk estimates

Loss to follow-up was low (2%); nevertheless, if any of the 12 whose vital status was not ascertained did die of lung cancer, the calculated

SMRs would be lower than they should be, and therefore the risk estimates derived by DHS would also be too low.

One of the lung cancer deaths in the middle exposure category was originally miscoded as a non-lung cancer death. For consistency with the comparison population (general population rates inevitably include some miscodings of the cause of death), this death should not be counted as being due to lung cancer. In this risk assessment, the estimates were calculated by excluding this death. A comparison showed that inclusion of this death as due to lung cancer did not substantially alter the risk estimates.

The original analysis of Thun et al. (1985) used U.S. lung cancer death rates for comparison with this cohort (Table VII-9) because state rates were not available before 1950. An updated report (Thun et al. 1986) includes estimates of SMRs based on Colorado rates in which the 1950 rates were assumed to hold for the earlier years (Tables VII-10). The DHS estimated excess risk using both the U.S. and Colorado lung cancer death rates. As shown below, these estimates are virtually identical.

Uncertainty with regard to the measures of risk reported by Thun et al. are rather minor. With the exception of the unknown outcomes for those lost to follow-up, DHS staff has incorporated these uncertainties (stemming from the miscoding and the choice of control population) into its analysis.

(iii) Nature of the cohort and occupational exposure

The exposures of the workers in the study tended to be acute and occurred within a short time span, while those of the general population occur at low levels over a lifetime. It may be that a high, short-term exposure which overwhelms the body's defense mechanisms is necessary for cadmium to exert its carcinogenic effect. There is no clear evidence, however, that cadmium operates in this way. In an animal study, at an exposure level of 1.6 mg/m^3, initial pulmonary damage appeared to be repaired even under continued exposure (Hart, 1986). Therefore, DHS has made the health-conservative assumption that cumulative exposure is the appropriate measure for evaluating the dose-response relationship between cadmium and lung cancer mortality.

Since white male workers in Colorado constitute the members of the cohort, in order to estimate risks to the general California population it has been assumed that dose-response relationships observed in Colorado white male workers are applicable to California residents of all ages, including: nonwhites, females, and nonworkers. DHS staff has used a model which quantifies the overall health difference between the workers in the study and those in the general population of the same race, sex and age. That is, an estimate was made not only of cadmium's carcinogenic potency, but also of the "healthy worker effect". In effect, this risk assessment assumes that the dose-response relationship established for white males in the general population of the same ages as the workers is applicable to white males of other age groups and to females and nonwhites of all ages. The DHS staff knows of no way to quantify the uncertainty stemming from this assumption.

(iv) Confounding

Uncertainty stemming from potential confounding by smoking or arsenic has been discussed in detail elsewhere in this document (See Section VII.J.2 Human Studies, Respiratory Cancer : Thun study).

b. Modeling of the Data for Cancer Risk Assessment

(i) Exposure assumptions for the modeling

As discussed above, the first assumption of the risk assessment is that the lifetime cumulative exposure to cadmium can be used as a summary measurement for determining carcinogenic potency. In other words, it is assumed that total lifetime dose determines cancer risk, regardless of whether it is inhaled in a workplace setting at the mg/m^3 level, or whether it is inhaled over a whole lifetime from ambient air at the ng/m^3 level. The DHS staff recognizes that this is a simplistic assumption and that dose-rate may influence the magnitude of carcinogenic effects. In the case of cadmium, the data are insufficient to quantify the dose-rate effect on carcinogenesis. The assumption to ignore dose-rate is a health-protective assumption since the environmental exposures involve lower dose-rates than were prevalent among the workers. The median cumulative exposure in each of the three exposure groups designated by Thun et al. was used in the risk assessment (see Table IX-3). (These medians, though not in the published report, were provided by Dr. Thun, personal communication.)

Table IX-3

EXPOSURE LEVELS OF
WORKERS IN STUDY BY
THUN ET AL.

	Cumulative Exposure in mg-days/m^3			Equivalent Lifetime Dose Rate* in $\mu g/m^3$
	Range Reported by Thun et al.	Median	Median Adjusted for 240 Workdays/year	Median
Low	≤584	280	184.1	2.7
Middle	585-2920	1210	795.6	11.8
High	≥2921	4200	2761.6	41.0

* Assumes 24 hours/day exposure and an estimated average lifetime of 61.5 years.

A second assumption regarding exposure is that particle size distribution in the occupational setting of the Thun et al. study is similar to that of ambient California air. There is insufficient information to determine the validity of this assumption, or to determine whether this assumption leads to an underestimate or overestimate of actual risk.

(ii) Justification of model

A linear model which incorporates a parameter for the "healthy worker effect" was fitted to the data and evaluated for goodness-of-fit. DHS staff considers linear models most appropriate for extrapolating human cancer risks at low doses from human data at high doses. This position is based on the view that risk estimates should represent plausible upper bounds. The concept of a "plausible upper bound" is distinct from a "worst-case scenario," as explained below.

Current scientific opinion supports the view that the assumption of linearity is likely to be health-conservative, and should therefore lead to an upper bound estimate of low-dose risks. The actual risks may be lower than those estimated, but are unlikely to be higher, though this possibility cannot be completely ruled out. Therefore the "upper bound" aspect of the DHS staff risk estimate is mainly a reflection of the linearity assumption.

On the other hand, the use of observed mortality data and reasonable exposure estimates renders these estimated risks plausible. If the estimates of exposure had been based on assumptions that were extreme (e.g., only using the lowest measurements, thereby inflating the potency estimate) or if instead of the observed deaths, an upper confidence limit had been used, then the resulting risk estimates would have been derived from a "worst case scenario." Therefore the "plausible" aspect of the DHS risk estimate stems from the use of available and reasonable estimates of exposure and observed mortality data.

Finally, the use of the slope estimated by an iterative least squares (Gauss-Newton) method yields a best estimate for a plausible upper bound of risk. The 95% (two-tailed) upper confidence limit on the slope of the linear model yields an upper confidence limit for the risk estimate. It represents, under the assumption of linearity, an estimate of slope that is likely to be too low only 2.5% of the time.

(iii) Specification of model

A Poisson regression model was fitted to the data. In this model the observed deaths are a function of two variables: the dose and the expected deaths. The function has two parameters: one for the carcinogenic potency of cadmium, the other to account for the healthy worker effect.

Let Obs_i = observed deaths in exposure group i

Exp_i = expected deaths in exposure group i based on the indirect method of age adjustment

d_i = median dose received by group i

Then the model is expressed as:

$$E[\ Obs_i] = (1+\beta d_i) \cdot \alpha \cdot Exp_i$$

where $E[\cdot]$ represents the expectation of a random variable,

α = healthy worker effect, and

β = potency of cadmium per unit dose.

This model predicts that in the absence of cadmium exposure (d_i=0), the observed deaths will equal the expected deaths times some factor which distinguishes the workers from the general population, a factor which can be termed the "healthy worker effect." The appropriateness of this model is indicated by the mortality experience of the low exposure group, which had an SMR for lung cancer of 53. (The cohort also had a low SMR for cardiovascular deaths.) This model therefore separates the carcinogenic effect of cadmium from the opposing, healthy worker effect. Using the nonlinear regression procedure (NLIN) of the statistical package produced by the SAS Institute, the parameters were estimated at:

$\hat{\alpha}$ = .500 (unitless parameter) and

$\hat{\beta}$ = .0017 (cumulative mg-days/m^3)$^{-1}$.

The 95% (two tailed) upper confidence limit for β was .0079, and the χ^2 goodness-of-fit statistic was .15 (1 df, p=.70). Lung cancer deaths predicted by the model are compared with the observed lung cancer deaths for the three exposure groups in Table IX-4.

Table IX-4

LUNG CANCER DEATHS
AMONG CADMIUM-EXPOSED WORKERS:
OBSERVED AND PREDICTED

		CUMULATIVE EXPOSURE GROUPS		
		Low	Middle	High
OBSERVED *		2	6	7
PREDICTED:	LINEAR RELATIVE RISK MODEL WITH			
	HEALTHY WORKER EFFECT			
	U.S. Controls	2.49	5.48	7.23
	Colorado Controls	2.48	5.50	7.22
	NO HEALTHY WORKER EFFECT			
	U.S. Controls	4.16	6.69	6.42[a]
OBSERVED[b]*		2	7	7
PREDICTED:	LINEAR RELATIVE RISK MODEL WITH			
	HEALTHY WORKER EFFECT			
	U.S. Controls	2.94	5.99	7.44

* Data of Thun et al. 1985

a The prediction of fewer deaths in the high exposure group than in the middle exposure group reflects a larger number of person-years in the middle exposure group.

b The lower part of this table represents the Thun et al. data in which an originally miscoded death has been corrected to be due to lung cancer.

As discussed above (Section IX.B.2.a.ii Uncertainties in the risk estimates), the uncertainties in the data (due to miscoding of one lung cancer death and the use of U.S. rather than Colorado population rates) were evaluated by fitting two alternate versions of these data. In addition, the model was altered by removing the healthy worker parameter, for the purpose of comparison. (See Table IX-4.):

(1) Using expected deaths based on Colorado rates rather than U.S. rates, the predicted deaths were almost identical, though the estimate of α was different ($\hat{\alpha}$ = .727, not shown in table). The model therefore behaves as it should, i.e.: (1) the estimate of the dose effect should not depend on the comparison population; (2) the difference between these workers and the population of Colorado should be less than the difference between the workers and the U.S. population (that is, $\hat{\alpha}$ was closer to 1 using the Colorado population).

(2) Inclusion of the miscoded lung cancer death from the middle dose group (i.e. fitting the model to observed deaths of 2,7 and 7 rather than 2,6 and 7 for the three dose groups) yielded very similar results.

(3) For comparison, the linear model without a healthy worker parameter was fitted to the data. As seen in Table IX-4, the fit was not as good, particularly for the low dose category.

c. Application of the model to the California population

With these estimates of the parameters, the model was then applied to the California population to predict the excess number of lung cancer deaths

induced by cadmium exposure. The mathematical details are shown in appendix D.

First, a current life table was produced for California males and females separately, using five-year age intervals (see Table D-1a and D-1b). The life table allows one to adjust for competing causes of mortality in evaluating the risks due to a particular cause. The background hazard of lung cancer death for each five-year age interval was calculated using 1980 census data for California (Bureau of the Census, 1982) and age-specific death rates for California from 1979-80 vital statistics data (California Department of Health Services, 1982) by standard statistical techniques (Chiang 1984). These were then summed over a lifetime: the last entry of the last column in Table D-1a and D-1b represents, for males and females respectively, the cumulative probability of dying of lung cancer to the end of that age interval, i.e. age 79.

Next, using the estimated value for β and setting $\alpha = 1$ for the general population (i.e. no healthy worker effect), the hazard of lung cancer death given a continuous lifetime exposure to 1 ng/m^3 cadmium was calculated from the model. Using these hazard rates, a new life table was constructed (Tables D-2a for males and D-2b for females). Subtracting the background probability of a lung cancer death from that obtained for an exposed population results in a unit risk of 1.6 excess lung cancer deaths per million persons in California due to a continuous lifetime exposure of 1 ng/m^3 cadmium in air. Table IX-5 summarizes these risk estimates.

TABLE IX-5

LIFETIME PROBABILITY OF
LUNG CANCER DEATH

	MALES	FEMALES	
BACKGROUND	.0554577	.0248524	
EXPOSED[a] no lag			
LSE[b]	.0554599	.0248534	
UCL[c]	.0554731	.0248593	
EXPOSED[a] 10 year lag			
LSE	.0554595	.0248532	
EXCESS DUE TO EXPOSURE			TOTAL[d]
LSE	2.2×10^{-6}	1.0×10^{-6}	1.6×10^{-6}
UCL	15.4×10^{-6}	6.9×10^{-6}	11.6×10^{-6}

[a]Exposed continuously to 1 ng/m^3 Cd in ambient air.
[b]LSE = least squares estimate.
[c]UCL = 95% upper confidence limit.
[d]Assumes 50% of population for each sex.

Using the upper confidence limit for β instead of the least squares estimate yields an upper limit of 11.6×10^{-6} for the unit risk of excess lung cancer deaths per 1 ng/m^3 cadmium in air (based on Tables D-3a and D-3b). An alternative analysis which assumes that the effect of an exposure on subsequent lung cancer deaths requires a 10-year latency period did not alter the estimates of excess risk (see Tables D-4a and D-4b).

The estimated unit risk for excess lung cancer deaths due to 1 ng/m^3 lifetime exposure of cadmium is 2×10^{-6}. The upper 95% confidence limit of this estimate is 12×10^{-6}.

The DHS staff recommends that the upper 95% confidence limit estimate be used for regulatory purposes, rather than the best estimate, for two reasons: (1) the epidemiologic evidence is suggestive of cadmium carcinogenicity for several urogenital sites, and (2) the application of a dose-response relationship observed in adult working males to the general population assumes equal potency across all ages and both sexes.

This risk assessment uses only one site, respiratory tract cancers. As stated in Section VII.J.2, there is evidence suggesting an association between cadmium exposure and renal, bladder, and prostate cancer. Since quantitative exposure data were not available for those studies that showed increased risk for these cancers, it was not possible to conduct an analysis similar to that conducted for respiratory cancer. Deaths from these three cancers are much

rarer than respiratory cancer deaths, and the excess number of deaths from all three combined is likely to be far less than the number of excess respiratory cancer deaths for a given level of cadmium exposure. Nevertheless, some margin above the least squares estimate of unit risk would be desirable, in order to include the added risk for deaths from cancer at other sites.

The assumption of equal potency for cadmium carcinogenicity across all ages and both sexes could result in underestimates of risk for several reasons. Rapidly proliferating tissues may be more susceptible to carcinogenic agents than cells which are proliferating at a slower rate since the opportunities for errors in DNA replication are greater at these times. Lung growth occurs through childhood and puberty. Secondly, where air concentrations of cadmium are related to dust from contaminated soil, children are not only closer to the ground, but far more likely to play in dirt and thus to have substantially higher exposures than adults. Thirdly, a recent paper by Phalen et al. (1985) showed that tracheobronchial particle deposition is generally more efficient in smaller (younger) individuals than in larger (older) people. For instance, the dose on a per kg mass basis for 5 μm diameter particles could be 6 times higher in a resting newborn than in a resting adult. Therefore, at ages when individuals are potentially more susceptible to carcinogenic damage, they may be consistly receiving higher exposures and distributing cadmium to the target site more efficiently.

For these reasons the DHS staff recommends adoption of the upper confidence limit on the unit risk, i.e. 12 excess lifetime cancer deaths per million persons.

3. Comparison of Animal- and Human-Based Risk Estimates

A comparison of the two risk assessments, one based on animal data, the other based on human data, is shown in Table IX-6 and in Figure IX-2. Comparing the low-dose risk estimates from both sets of data, it can be seen that the multi-stage model applied to lung tumors in male rats predicts about 60-fold greater excess lung cancer deaths at ambient exposure levels than a linear extrapolation from respiratory cancer deaths among the occupational cohort. The maximum likelihood animal-based estimate is about one order of magnitude larger than the upper confidence limit for the human-based estimate.

Considering the degree of uncertainty associated with extrapolation over 3-4 orders of magnitude, the differences between the two risk assessments are relatively small. Nevertheless, the ranges of risk provided by these two sources of data do not overlap. Staff members of DHS believe that the human-based risk assessment should be adopted. In reaching this decision, we have considered the following possible explanations for the difference between the two risk assessments:

(1) If the doses received by the workers were overestimated, then the potency would be underestimated by the human-based risk assessment, since the observed number of cancer deaths is fixed.

Members of DHS staff, in consultation with industrial hygiene staff of Cal/OSHA, have examined the methods used to estimate exposure levels

TABLE IX-6

ANIMAL AND HUMAN BASED PREDICTIONS

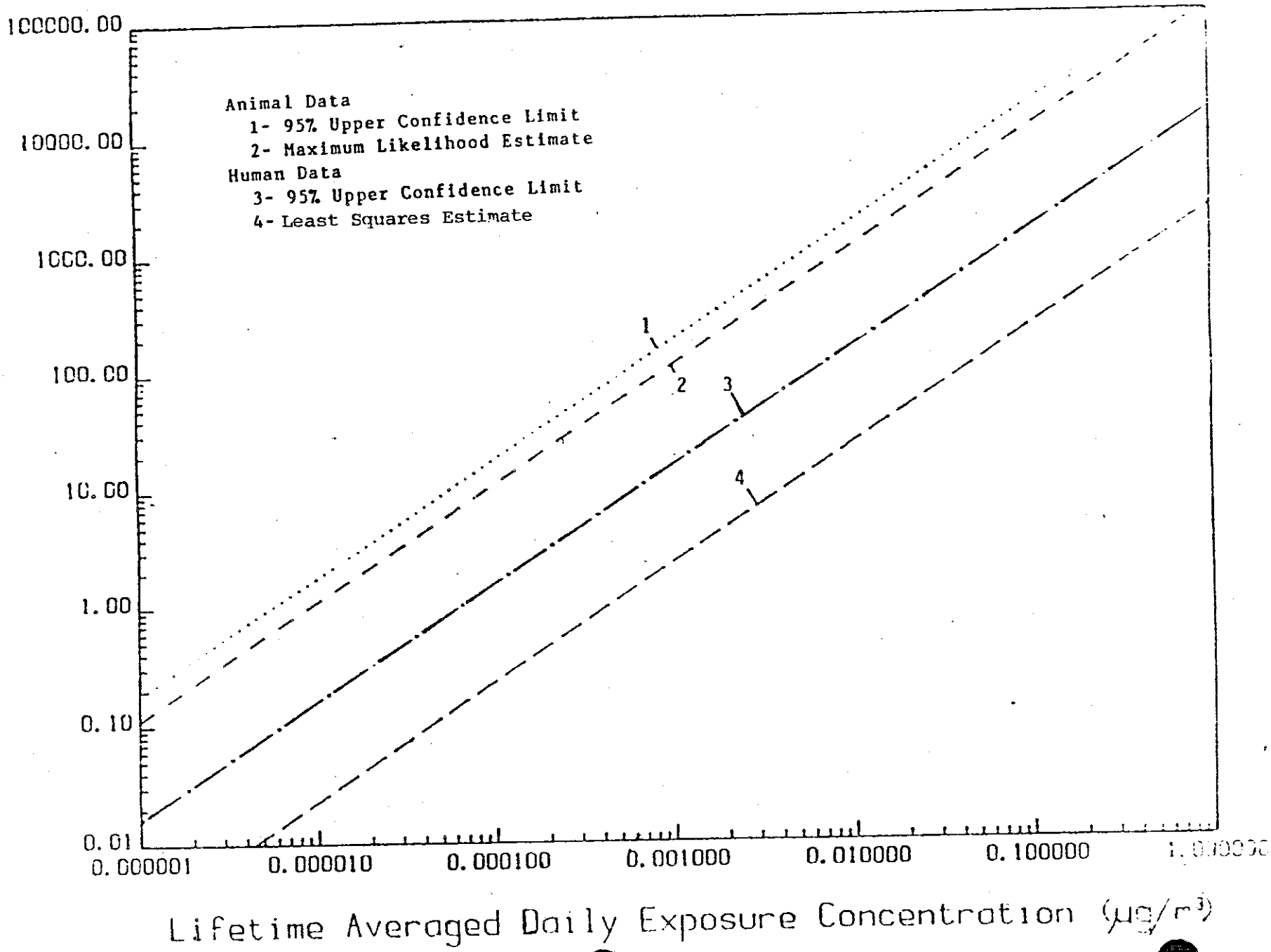
OF EXCESS LIFETIME CANCER RISKS PER MILLION PERSONS

EXPOSED TO AMBIENT AIRBORNE CONCENTRATIONS OF CADMIUM

	Ambient Air Concentration		
	1 ng/m^3	2.5 ng/m^3	40 ng/m^3
	Overall mean in California	UCL of overall California mean	hot spot mean
ANIMAL DATA			
95% Upper Confidence Limit	$180/10^6$	$450/10^6$	$7200/10^6$
Point Estimate	$110/10^6$	$275/10^6$	$4400/10^6$
HUMAN DATA			
95% Upper Confidence Limit	$12/10^6$	$30/10^6$	$480/10^6$
Point Estimate	$2/10^6$	$5/10^6$	$80/10^6$

Figure IX-2

Estimates of Human Excess Lifetime Cancer Risk Based on Animal and Human Data



reported by Thun et al. (1985), Smith et al. (1980a,b). We have concluded that the exposure levels were not likely to have been overestimated. In fact, a number of assumptions may have resulted in underestimates of past exposures. Underestimation of potency due to inaccuracies in the worker exposure data is therefore, unlikely.

(2) If the risk of respiratory cancer in cadmium-exposed workers were underestimated, then the human-based risk assessment may be too low. This could have occurred for three reasons.

The first is that the U.S. general population may not have been the most appropriate comparison population for this worker cohort. A better choice may have been the population in the state of Colorado, or perhaps that of the county where the factory was located, both of which have lower respiratory cancer mortality rates (10 to 25%) than the U.S. population (Thun et al. 1985, NIH 1975). As shown in Table IX-3, however, the use of Colorado controls did not affect the potency estimates because the model that was adopted was robust to the choice of comparison population.

The second reason that respiratory cancer risk for exposed workers could have been underestimated is that the follow-up period may have been too short to allow for the latency period. The animal studies indicated a long latency for cadmium-induced lung tumors: 23 out of 25 tumors appeared in high-dosed animals, which died after 27 months. (Had the study been terminated at 24 months, the typical length of a bioassay, these

tumors might not have been observed.) The epidemiology also indicated long latencies: 20+ years (Lemen et al. 1976) and 30+ years (Sorahan and Waterhouse 1983). Since 83% of the workers had been followed for at least 20 years and 66% had been followed for at least 30 years, the latency period for a large proportion of the lung cancers had probably passed.

The third reason that respiratory cancer risk for exposed workers could have been underestimated is if incidence and mortality differed greatly, either due to long survival with the disease, or to cure. Since lung cancer is usually fatal, having a five-year survival rate of about 10% for U.S. whites (Silverberg and Lubera 1983), it seems unlikely that the risk of respiratory cancer has been significantly underestimated because of nonfatal cases of respiratory cancer.

Because the risk estimates from the human data do not appear to be too low, the staff of DHS concludes that a significant underestimate of human carcinogenic response from cadmium exposure is not likely.

Based on examining points (1) and (2), and the fact that a linear model is likely to be health-conservative, DHS staff concludes that the estimates of human carcinogenic potencies for cadmium shown in Table IX-2 are not too low, and that the higher potency estimate derived from animal data must be explained by other arguments.

(3) If rodents and humans differ in their sensitivities to the carcinogenic effects of cadmium, then part of the discrepancy may be due to interspecies differences. These interspecies differences are likely to stem from different rates and pathways of distribution, metabolism and excretion (Williams 1978).

However, there is no evidence to suggest large differences in these processes between humans and other species (See Section V).

(4) If the conversion factor in calculating human equivalent doses from the animal bioassay were inappropriate, then the animal-based estimates of potency would be too high.

As discussed earlier in this section (IX.B.1), the interspecies conversion is based on surface area equivalence. Use of this conversion method has been justified by the argument that: (a) the metabolic rate determines the carcinogenic activity of the compound or its reactive metabolite; and (b) body surface area is related to metabolic rate.

In the case of cadmium, it could be argued that metabolic rate is not relevant since the main site of action (and the site used for these risk assessments) is the point of contact. Based on direct airborne concentrations (in $\mu g/m^3$) (averaged over lifetime), the staff of DHS recalculated the slopes of the animal-based extrapolation using the multistage model. The effect was to reduce the slope by more than one

order of magnitude, resulting in low-dose risks almost identical to those predicted by the upper confidence limit of the human-based risk estimate.

It is possible, therefore, that the discrepancy between the animal- and human-based risk assessments may be explained by an inappropriate choice of interspecies conversion factor. This issue, however, cannot be resolved given the current state of knowledge.

(5) If the greater carcinogenic response in animals were due to administration of cadmium chloride rather than the compound to which the cohort of workers was primarily exposed, cadmium oxide (Thun et al. 1985), then a direct extrapolation from the animal bioassay data would not be appropriate for ambient human exposures to cadmium oxide. A greater potency for the soluble cadmium chloride could explain the discrepancy. The pharmacologic evidence does not support this thesis, however, since animal studies indicate cadmium chloride and cadmium oxide are handled in a similar fashion by the respiratory tract (Oberdörster 1979, 1980).

(6) If the dose rate affected potency, then a lower dose rate administered over a lifetime might carry a different risk than a higher rate administered for short periods. In this case, the animals received the continuous lifetime dosing, while the workers received higher, short-term exposures. Since it does not seem likely that a lower potency would result from higher short-term exposures, dose rate probably does not explain the different risk estimates.

Members of DHS staff have concluded that the discrepancy between the animal- and human-based cadmium risk estimates is not due to deficiencies in the human data for exposure or response. Thus, reliance on the human-based risk assessment is sufficiently health-conservative because of the assumption of linearity between dose and excess relative risk. Because there may be subgroups of the population whose sensitivity to the carcinogenic effects of cadmium is greater than adult white males, and because there may be a small added risk for cancers at other sites due to cadmium exposure, the use of the upper 95% (two-tailed) confidence limit for risk is recommended. This risk is estimated at 12 excess lifetime cancer deaths per million persons continuously exposed to 1 ng/m^3 cadmium throughout their lifetimes.

C. Estimated Risks at Ambient Airborne Concentrations of Cadmium

The noncarcinogenic and carcinogenic risk assessments performed in the previous sections (IX.A and IX.B) apply to general situations. In order to estimate the hazard posed by airborne cadmium to residents of California, it is necessary to determine what the ambient concentration is. The staff of the Air Resources Board has estimated that the range of average ambient concentrations is from 1 to 2.5 ng/m^3.

As discussed in Section IX.A, lifetime exposure to an ambient airborne concentration of 1 ng/m^3 does not pose a significant hazard for renal toxicity. The ambient airborne concentration of 2.5 ng/m^3 is also two to three orders of magnitude less than the estimated ambient airborne concentration of cadmium (650 to 2500 ng/m^3) necessary to induce renal toxicity in 10 percent of the

population. Therefore, this ambient concentration is not expected to pose a significant health hazard. Since renal toxicity is believed to be the most sensitive noncarcinogenic effect caused by cadmium, no other noncarcinogenic effects are expected to occur at the present ambient levels.

The carcinogenic risk from cadmium exposure has been estimated based on the assumption that the mechanism of action is a nonthreshold process. Therefore, there is always an excess cancer risk from exposure to any level of cadmium. As discussed in Section IX.B, staff members of DHS have concluded that the best estimated range of risk for excess lifetime cancer is from 2×10^{-6} to 1.2×10^{-5} $(ng/m^3)^{-1}$. The theoretical excess lifetime cancer risk from continuous 24-hour per day exposure at the average concentrations of 2.5 ng/m^3 in California ambient air is 1 to 30 per million persons exposed (See Table IX-6).

The ARB has also identified hotspots in California where ambient exposures are 40 ng/m^3, 24-hour average. The range of estimated excess lifetime cancer risk due to the average hot spot exposures is 80 to 480 per million persons exposed. The ARB staff estimates that approximately 57,000 people in California reside in these hot spots.

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Appendix A

Carcinogenicity of Cadmium Chloride Aerosols in W Rats [1,2]

Shinji Takenaka,[3,4] Hubert Oldiges,[3] Hans König,[3] Dieter Hochrainer,[3] *and* Günter Oberdörster[3,5,6]

ABSTRACT—Lung cancers were induced in inbred W rats by cadmium chloride aerosols. For 18 months, 120 male W rats were continuously exposed to cadmium chloride aerosols with cadmium (Cd) concentrations of 12.5, 25, and 50 μg/m³, respectively. For the same period of time, 41 rats were kept in filtered air; these rats served as the control group. The survivors were killed 13 months after the end of the inhalation experiments. Histopathologic examination revealed a dose-dependent incidence of primary lung carcinomas of the following types: adenocarcinomas, epidermoid (squamous cell) carcinomas, combined epidermoid carcinomas and adenocarcinomas, and mucoepidermoid carcinomas. The incidence of lung carcinomas was 71.4% in the group exposed to 50 μg Cd/m³, 52.6% in the group exposed to 25 μg Cd/m³, and 15.4% in the group exposed to 12.5 μg Cd/m³. None of the controls developed lung carcinomas. At the end of the experiment, the remaining Cd concentrations in the lungs were relatively high, almost at the same level as those in the livers.—JNCI 1983; 70:367–373.

In recent years the incidence of lung tumors has increased markedly. Air pollution is assumed to be one of the reasons for this increase (*1, 2*).

Cadmium (Cd), frequently used in industry, is highly toxic. A number of toxicity experiments revealed acute and chronic disorders in the kidneys, bones, testes, and lungs of animals exposed to Cd (*3*). Although in some of the reports a relationship between lung tumors and Cd is suggested (*4–6*), it has not yet been confirmed experimentally.

A previous experiment (Oldiges H, Oberdörster G, Heering H, Hochrainer D, Mohr U: Unpublished data) in our institute and a publication by Hadley et al. (*7*) showed that 1 or 2 lung tumors developed in rats exposed to Cd aerosols. Since spontaneous, primary lung tumors seldom occur in rats, we thought these findings were important. Thus we performed a long-term inhalation experiment with cadmium chloride ($CdCl_2$) to ascertain its effects on rats.

MATERIALS AND METHODS

Inhalation system and aerosol generation.—The inhalation was performed according to a technique previously reported by Prigge and co-workers (*8, 9*) and Oberdörster et al. (*10*). The exposure took place in 225-liter inhalation chambers containing two wire mesh cages each comprised of 10 rats. We generated the aerosol by atomizing a solution of $CdCl_2$ (≈0.32 g/liter) with an ultrasonic atomizer. Since the consumption of the solution by the atomizer was 100 ml/hour, the solution was kept in a 10-liter reservoir, which was large enough for constant operation also during the weekend. The reservoir was refilled daily, except on Saturdays and Sundays, and the concentration was adjusted and checked by titration. The air flow through the atomizer was 700 liters/minute, and the droplets dried in less than 1 second. The aerosol flow through the inhalation chambers was kept at 80 liters/minute. For lower concentrations of Cd, the aerosol was diluted with filtered laboratory air. We determined the aerosol concentrations once or twice a week by drawing aerosol samples of about 1 m³ air from the intake and the exhaust of the chambers through membrane filters with a nominal pore size of 0.2 μm. Even particles smaller than this size are collected on such filters with a deposition rate of almost 100%. The mass of Cd on the filters was determined by atomic absorption spectrometry. The Cd concentrations in the chambers were assumed to be the arithmetic mean of the Cd concentrations measured simultaneously at the intake and the exhaust. The particle size distribution was measured by means of an aerosol centrifuge (*11*), where the particles were deposited on a strip of filter paper according to their aerodynamic diameter. This strip was cut into sections, and the mass of Cd on each section was determined by atomic absorption spectrometry. By the known calibration of the centrifuge, the particle size distribution could be determined. The aerodynamic mass median diameter was 0.55 μm, the arithmetic standard deviation was 0.48 μm, and the geometric standard deviation was calculated to be 1.8.

Experiment.—Male inbred W rats [TNO-W-75-SPF; i.e., from Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek (TNO), inbred Wistar 1974 (W-74), and specific pathogen-free (SPF)], purchased from F. Winkelman GmbH & Co., Borchen, Federal Republic of Germany, were used. They were approximately 6 weeks old and weighed 133–135 g at the beginning of the experiment. We divided 120 rats into 3 groups; 40 rats each were continuously (23 hr/day, 7 days/wk) exposed for 18 months to $CdCl_2$ aerosols with nominal Cd concentrations of 12.5, 25, and 50 μg/m³. (The measured concentrations and frequency of measurements are shown in table 1.) In addition, 41 rats were kept in filtered air as a control group for the same period of time. Both experimental and control animals received water ad libitum and were given a pellet diet from 4 p.m. to 8 a.m. only to minimize food contamination with

ABBREVIATIONS USED: H & E=hematoxylin and eosin; NBS=National Bureau of Standards; PAS=periodic acid–Schiff; SRM=standard reference material.

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TABLE 1.—*Nominal and measured Cd concentrations of the $CdCl_2$ aerosols used for inhalation*

Nominal concentrations, $\mu g/m^3$	Measured concentrations, $\mu g/m^3$	Standard deviation, $\mu g/ml$	No. of measurements
50.0	50.8	5.9	212
25.0	25.7	3.6	220
12.5	13.4	2.1	210

$CdCl_2$. After the inhalation period, all rats were housed singly in plastic cages under conventional laboratory conditions for 13 months. During the experimental period, the animals were weighed every 3 months. Dead or dying animals were autopsied as soon as possible after they were detected. The rats surviving 31 months after the beginning of the experiment were killed by exsanguination under pentobarbital anesthesia for histopathologic examination and for measurement of the Cd content in their lungs, livers, and kidneys.

All tissues were fixed in 10% buffered Formalin. The skulls of the rats killed were decalcified in a mixture of formic acid and Formalin. The Paraplast sections (3–4 μm) for histopathologic examination were stained with H & E and by the PAS reaction.

A 0.2-g portion (wet wt) of lungs, livers, and kidneys was digested with 5 ml nitric acid (65% Suprapur; E. Merck A.G., Darmstadt, Federal Republic of Germany) under pressure at 170°C. After the removal of HNO_3, the residue was diluted to 10 ml with 1% nitric acid. NBS SRM 1577 (bovine liver; authentic Cd content: 0.27±0.04 μg/g; measured: 0.32±0.03 μg/g) was treated in the same way. The Cd concentration was determined on a Perkin-Elmer 4000 spectrometer equipped with an HGA 500 graphite atomizer and an AS 40 autosampler. The Massmann furnace was modified by the application of a L'vov platform to reduce interferences of the biological matrix and to achieve a higher sensitivity (*12–14*). For the same purpose a 5% solution of $NH_4H_2PO_4$ (E. Merck A.G.; guaranteed reagents for analysis) was added to the sample injected into the cuvette. All measurements were done in the standard addition mode.

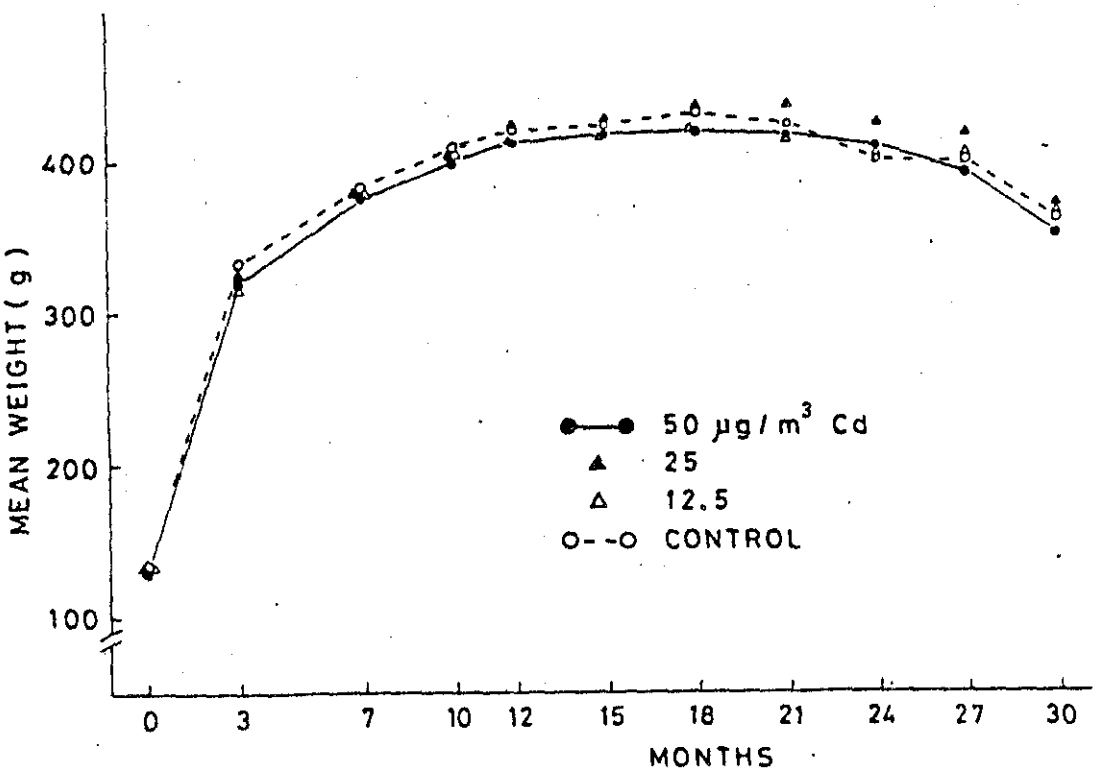
The sensitivity of the Cd determination was 1 ng Cd/ml, and the corresponding absorption value was 0.073 (absorbance of 16.6%) for a 20-μl sample.

RESULTS

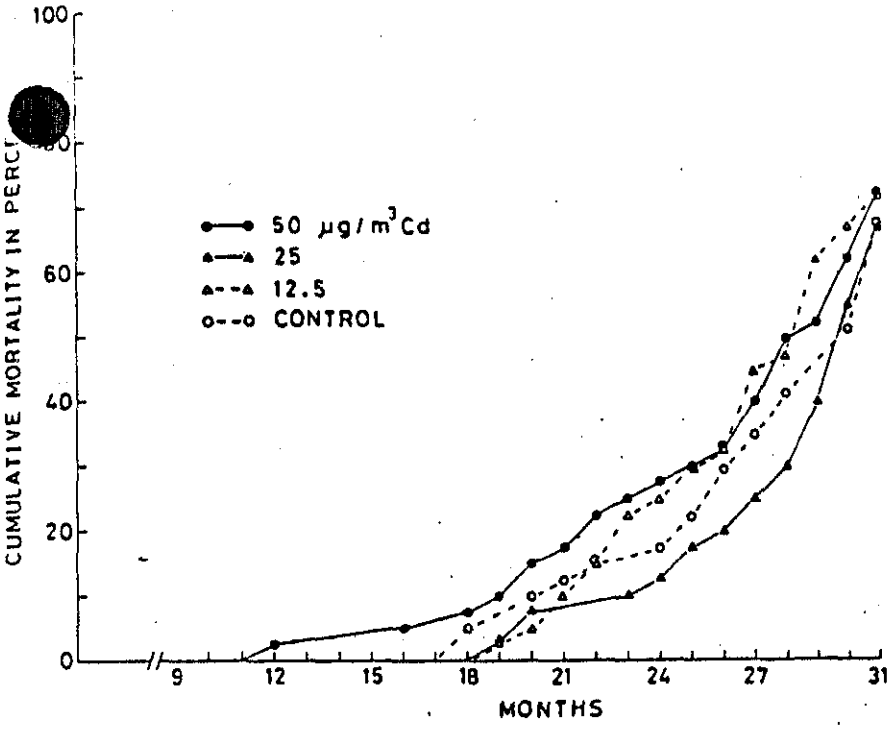
During the inhalation period of 18 months, the body weights were similar among the control and the $CdCl_2$-exposed groups. Six months after the inhalation period, all rats had lost weight, which kept on decreasing until the end of the experiment. However, there were no significant differences among the 4 groups (text-fig. 1).

The mean survival times (in wk, ± SD) were 121.9±18.9, 119.2±16.9, 124.5±15.4, and 116.1±22.9 for the control group and the groups exposed to Cd at 12.5, 25, and 50 $\mu g/m^3$, respectively. The mean values include the lifetime of rats killed when the experiment was terminated. The differences were not significant, though the mean survival time of the rats exposed to 50 μg Cd/m^3 was slightly shorter than the mean survival times of the other groups (text-fig. 2).

As shown in table 2, the Cd concentrations in the lungs were 10.4 μg/g wet weight in the highest, 4.7 μg/g in the middle, and 5.6 μg/g in the lowest concentration groups and less than 0.03 μg/g in the control group. The values in the lungs and livers were comparable. The Cd concentr...



TEXT-FIGURE 1.—Average weights of rats in the indicated exposure groups



TEXT-FIGURE 2.—Mortality of rats in the [illegible] exposure groups.

tions in the kidneys were about three times as high as those in the other organs examined.

The first epidermoid carcinoma occurred in a rat exposed to 25 μg Cd/m³; this rat died 20 months after the beginning of the experiment. The first adenocarcinoma was seen in a rat exposed to 12.5 μg Cd/m³; this rat died after 22 months. In 2 rats of the group exposed to 50 μg Cd/m³, which died after 23 months, a lung adenocarcinoma and lung epidermoid carcinoma, respectively, were observed.

The adenocarcinoma, mainly showing papillary and sometimes glandular structures, had developed in every lung lobe. It consisted of cuboidal and columnar cells with irregular nuclei and infrequent mitoses. In many cases mucus secretion was noted (figs. 1–3).

The epidermoid carcinoma occurred as a single tumor mass consisting of typical epidermoid structures, with or without keratinization, and frequent mitoses (figs. 4, 5).

The mucoepidermoid carcinoma showed mucus-secreting cells in the cell nests of epidermoid structures (fig. 6).

Most of the tumors were multiple. Two different types of carcinomas (adenocarcinoma and epidermoid carcinoma) occurred in the lung of 1 rat each of the groups exposed to 25 and 50 μg Cd/m³ (fig. 7).

TABLE 2.—*Concentration of Cd in lungs, livers, and kidneys of W rats exposed to $CdCl_2$ for 18 months (13 mo after the end of the inhalation)*

Exposure groups	No. of rats	Cd concentration, μg/g wet wt, in:[a]		
		Lungs	Livers	Kidneys
Control	9	<0.03	0.1±0.1	0.3±0.1
12.5 μg Cd/m³	6	5.6±1.0	2.2±0.6	13.5±3.2
25 μg Cd/m³	9	4.7±1.5	5.9±1.5	16.4±3.6
50 μg Cd/m³	9	10.4±4.2	13.5±3.0	33.6±10.7

[a] Results are means ± SD.

In all, primary lung carcinomas were induced in 71.4% (25/35 rats examined histopathologically) of the animals exposed to 50 μg Cd/m³, 52.6% (20/38 rats) of the animals exposed to 25 μg Cd/m³, and 15.4% (6/39 rats) of the animals exposed to 12.5 μg Cd/m³. Table 3 shows the distribution and histologic types of the tumors induced. In addition, metastases in the regional lymph nodes and kidneys and invasion into the regional lymph nodes and the hearts were observed in some of the cases. Also, several rats of the exposed groups showed lung adenomas and adenomatous hyperplasia in the bronchoalveolar area (fig. 8). The control group did not develop any lung tumors, although 2 control rats had metastases deriving from a skin epidermoid carcinoma and a skin fibrosarcoma, respectively.

Many rats in every group also showed various tumors in organs other than the lung. There were pituitary tumors (4 in the control group, 12 in the group exposed to 12.5 μg Cd/m³, 5 in the group exposed to 25 μg Cd/m³, and 1 in the group exposed to 50 μg Cd/m³), thyroid C-cell tumors (2 in the group exposed to 12.5 μg Cd/m³ and 1 in the group exposed to 25 μg Cd/m³), malignant or benign pheochromocytomas (2 in the control group), 8 in the group exposed to 12.5 μg Cd/m³, 4 in the group exposed to 25 μg Cd/m³, and 4 in the group exposed to 50 μg Cd/m³), pancreatic islet cell tumors (1 in the control group and 1 in the group exposed to 50 μg Cd/m³), testicular Leydig cell tumors (4 in the control group, 1 in the group exposed to 12.5 μg Cd/m³, 1 in the group exposed to 25 μg Cd/m³, and 2 in the group exposed to 50 μg Cd/m³), skin tumors (3 in the control group, 2 in the group exposed to 12.5 μg Cd/m³, 3 in the group exposed to 25 μg Cd/m³, and 2 in the group exposed to 50 μg Cd/m³), and systemic tumors (1 myelomonocytic leukemia in the control group, 1 histiocytoma, 1 hemangiosarcoma, and 1 malignant schwannoma in the group exposed to 12.5 μg Cd/m³, and 1 malignant lympho[illegible] in

TABLE 3.—*Lung changes in W rats after exposure to $CdCl_2$ aerosols*

Exposure groups	Initial No. of rats	No. of rats examined histologically	No. of rats with lung changes						
			Adenomatous hyperplasia	Adenoma	Total (%) carcinomas	Adenocarcinoma	Epidermoid carcinoma	Mucoepidermoid carcinoma	Combined epidermoid carcinoma and adenocarcinoma
Control	41	38[a]	1	0	0	0	0	0	0
12.5 μg Cd/m^3	40	39[b]	6	1	6 (15.4)	4	2	0	0
25 μg Cd/m^3	40	38[c]	5	0	20 (52.6)	15	4	0	1
50 μg Cd/m^3	40	35[d]	3	1	25 (71.4)	14	7	3	1

[a] Two rats died during the first 18 mo; another rat was not examined because of autolysis.
[b] One rat was not examined because of autolysis.
[c] Two rats were not examined because of autolysis.
[d] Three rats died during the first 18 mo; 2 other rats were not examined because of autolysis.

the group exposed to 25 μg Cd/m^3). In addition, many rats of the control and the $CdCl_2$-exposed groups developed chronic nephrosis, cardiac fibrosis, and testicular atrophy. The occurrence of these histopathologic findings was not significantly different among the 4 groups. The nasal cavities of rats killed at the end of the experiment had neither hyperplastic changes nor tumors.

DISCUSSION

Numerous reports concerning the occurrence of Cd in the environment and its biological and health effects have been published. Acute exposure experiments with Cd aerosols have demonstrated that Cd damages alveolar type I cells, which are then replaced by proliferated alveolar type II cells (*15–18*). Subacutely inhaled Cd aerosols enhance cell proliferation in bronchi, bonchioli, and alveoli of the exposed rats (*9*). Although parenteral administration of Cd induces tumors in rats (local sarcomas and sometimes testicular tumors), evidence of carcinogenicity of inhaled Cd has not been demonstrated (*3, 19, 20*).

In our long-term experiment, lung cancer occurred at a high incidence, and a distinct dose-response effect was seen with $CdCl_2$ (71.4% lung cancer in the highest, 52.6% in the middle, and 15.4% in the lowest Cd concentration groups; no lung cancer in the control group). Histopathologically, such typical lung tumors as epidermoid carcinomas, adenocarcinomas, combined epidermoid carcinomas and adenocarcinomas, and mucoepidermoid carcinomas were observed. Several animals showed metastases or invasion to other organs.

Our success in demonstrating Cd carcinogenicity might be due to the following two reasons: 1) We chose long-term inhalation with $CdCl_2$ aerosols. Most of the other long-term studies were performed by use of parenteral injections or peroral administration. At the end of our experiment (13 mo after the cessation of the inhalation), the retained Cd contents in the lungs were still relatively high. Probably, a relationship exists between Cd retention in the lungs and its carcinogenicity. 2) The animals were continuously observed for a long period (31 mo). In the group exposed to 50 μg Cd/m^3, the first lung carcinomas were noticed 23 months after the beginning of the experiment. During the following 4 months we found no lung carcinomas; however, after the 27th month 23 lung carcinomas occurred, which means an incidence of more than 90% (only 2/25 examined rats were negative). If we had killed the animals before the 27th month, we would surely have detected initial stages of lung cancer, but not so many macroscopically and microscopically clear tumors.

As for parenteral or peroral administration of Cd, the kidney has already been proved to be the critical organ. It is estimated that a cortical Cd concentration of 200 μg/g wet weight might cause tubular dysfunction (*17*). In our experiment the average Cd concentration in the entire kidney of rats exposed to 50 μg Cd/m^3 amounted to 34 μg/g wet weight. Most of the animals in both the control and $CdCl_2$-exposed groups had chronic nephrosis—obviously an age-dependent change.

The results of this experiment demonstrate that exposure to $CdCl_2$ aerosols can cause lung carcinomas. It will now be necessary to investigate the pathogenesis of this lung cancer and to evaluate the critical or lowest Cd concentration that induces lung tumors.

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Appendix B

Low Dose Extrapolation Models

Low dose carcinogenic risk estimation is achieved by mathematical modeling which attempts to characterize an unknown relationship between exposure and the probability of response or to place an upper bound on that probability for a given exposure. Since this relationship cannot be observed at low doses, the models are fitted to data observed at higher doses (generally by estimating the model's parameters using maximum likelihood or other statistical methods). Extrapolating the fitted equation to low doses yields the estimated risk.

The two general classes of models are; tolerance distribution and mechanistic. Both types of models are used to fit dichotomous response data: cancer vs. no cancer. Each model describes the probability of a positive response, also termed the <u>risk</u>, as a mathematical function of dose d, denoted P{response given d} or more simply P(d). Any model can be modified to incorporate time as a predictor variable, i.e. a time-to-tumor or temporal model describes the probability of a positive response as a function of both time and dose, P{response at or before time t given d} again abbreviated P(d,t). Note that P(d) and P(d,t) include the background rates; they are <u>not</u> the excess probability of cancer due to the agent, but comprise the total risk.

Tolerance distribution models are based on the concept that each individual has a tolerance or threshold level, above which a response occurs. For each model, the variability in threshold levels among individuals in the population is described by a probability distribution.

Mechanistic models are based on a presumed biological mechanism of carcinogenesis. These models assume that a tumor originates from a single cell damaged by either the agent or its metabolites.

For purposes of risk assessment, "time-to-tumor" or temporal models are generally modifications of mechanistic models. For example, the Armitage-Doll or multistage model has been modified to include a Weibull function of time, referred to in DHS documents as the "Weibullized" multistage model.

1. Probit model

This model assumes that the sensitivities of individuals in the population follow a normal distribution when plotted against the log of the dose. Thus the probit function is a tolerance distribution model which predicts that the probability of cancer can be represented as:

$$P(d) = \Phi(a + b \ln d)$$

where $\Phi(x) = \int_{-\infty}^{x} (2\pi)^{-1/2} \exp(-u^2/2)du$, the cumulative standard normal distribution.

2. Logistic model or logit model

This model associates the log of the odds (=P{response}/P{no response}) of a carcinogenic response with a linear function in the log of the dose. The natural log (ln) of the odds is known as the logit. The equation for this model in terms of the logit is:

$$\ln \frac{P(d)}{1-P(d)} = a + b \log d$$

where log can represent the logarithm base 10 or base e.

The equivalent relationship in terms of risk is:

$$P(d) = [1 + \exp(-(a + b \log d))]^{-1}$$

which has no mechanistic basis in carcinogenesis and is therefore a tolerance distribution model.

3. <u>One hit model</u>

The mechanistic interpretation of this model states that one interaction between a molecule of the carcinogenic agent and the DNA in a single cell, is sufficient to induce cancer. This interaction can be viewed as a single "hit". The statistical description states that in this model, tolerances are proportional to an exponential density in some linear function of dose:

$P(d) = 1 - \exp[-(a + bd)]$ with constraints $a \geq 0$, $b > 0$. At low doses the risk is linear in dose i.e.:

$$P(d) = a + bd.$$

Thus, $P(d) - P(0) = bd$ is the excess probability of cancer.

As indicated below, there are three models which reduce to the one-hit model for certain values of their parameters: the gamma multihit model, the multistage model, and the Weibull model. In most instances the one-hit model generates the highest risk level for a given low dose, when compared to other models, but this will not hold for all cases. For instance, if the slope of the dose response curve rises steeply through most of the observed dose range, the Weibull and multihit models will fit a supralinear curve at low doses, predicting higher risks than the one-hit model predicts (Van Ryzin 1980, Van Ryzin and Rai 1980, Van Ryzin 1982).

4. Multistage model

This model is a generalization of the one-hit model. For cancer induction to occur, a cell must undergo a series of heritable changes, in which each change or stage is a prerequisite for the next. If there are k stages and if each dose-dependent change occurs as a linear function of dose, the model can be written as:

$$P(d) = 1 - \exp[-\prod_{i=1}^{k}(a_i + b_i d)].$$

This can be written in the more generalized form

$$P(d) = 1 - \exp[-\sum_{i=1}^{k} q_i d^i] \qquad \text{with } q_i \geq 0 \text{ for all } i.$$

When $q_i = 0$ for all $i \geq 2$, the multistage model reduces to the one-hit model. At low doses, lower order terms dominate and the curve is essentially linear with $P(d) = q_1 d$.

5. Weibull model

A Weibull distribution function, also known as the extreme value function, models the probability of response in relation to a power of the independent variable. This relationship is one of direct proportionality (to the power function) near zero. When dose is the predictor, the model takes the form:

$P(d) = 1 - \exp-(\lambda d^m)$ with $m>o$

$= 1 - \exp[-\exp(a+b \ln d)]$ where $b=m=0$ and $a=\ln \lambda$.

When m=1, the Weibull model reduces to the one-hit model. When m>1 the low dose behavior is concave (sublinear, slope increasing) and when m<1 the low dose behavior is convex (supralinear, slope decreasing).

6. Multihit model

The gamma multihit model is also a generalization of the one-hit model where carcinogenesis results from a sufficient number, or k, "hits" in a single cell within a specific time period. If the number of hits follows a Poisson distribution, then the probability of sufficient hits to induce carcinogenesis is: $P(d) = \sum_{x=k}^{\infty} \frac{(bd)^x e^{-bd}}{x!}$ which can be shown to equal $P(d) = \sum_{x=o}^{bd} \frac{x^{k-1} e^{-x}}{(k-1)!}$.

In practice, this model is extended to include non-integer values of k, in which case $P(d) = \int_{o}^{bd} \frac{x^{k-1} e^{-x}}{\Gamma(k)} dx$

where $\Gamma(k)$ is the gamma function:

$$\Gamma(k) = \int_{o}^{\infty} e^{-t} t^{k-1} dt \qquad \text{for all } k>0$$

$$= (k-1)! \qquad \text{for k a positive integer.}$$

When k takes nonintegral values, however, the mechanistic interpretation no longer applies.

The statistical description of this model states that tolerances follow a gamma distribution with parameters $(bd)^{-1}$ and k. When k=1, the multihit model reduces to the one-hit model. When k>1 the slope at low

doses is an increasing function, and when k<1 the low dose slope is a decreasing function.

7. Time-dependent models

As described, one can model the probability of a positive response as a function of both time and dose when P(d,t) = P[response before time t, given dose d]. One procedure is to modify a mechanistic model:

$$P(d,t) = f(d)\, g(t)$$

where f(d) can be any dose response model and g(t) is a function of time. The DHS has used a modification of the multistage model:

$$P(d,t) = 1 - \exp[-(\sum_{i=0}^{k} q_i d)(t-t_\ell)^h]$$

which, at low doses, reduces to the form

$$P(d,t) = q_i d\,(t-t_\ell)^h$$ where t_ℓ is the estimated latency time.

Since a Weibull function of time would be $\exp(-t^h)$, the above model for P(d,t) has been termed a Weibullized multistage model.

The theoretical basis for using the Weibull function of time lies in the observation of Armitage and Doll reported in their now classical paper of 1954, that the increase in cancer incidence over a lifetime is proportional to the sixth or seventh power of age, or time since birth.

It should be noted that "time-to-tumor" is a misnomer. It is the times-to-death with tumor which are observed. In practice, the advantage of using time-dependent models is greatest when the variation in survival times is large. Since animal experiments usually end with terminal sacrifice of a large proportion of the test animals, the actual survival time of most animals is not observed, and the advantage in modeling P(d,t) is small.

Rationale for Selection of Models for Extrapolation from Animal Bioassay Data

Theoretically, a model which best describes the biological processes would be the model of choice. However, neither cancer induction and promotion, nor detoxification and DNA repair mechanisms are understood well enough to provide an explicit form for a mathematical curve relating dose to cancer risk. Empirically, several different models can be fitted to most data sets, and it is unlikely that further experimentation, even with large groups of animals, will decisively discriminate between possible models.

The choice of mathematical models to represent dose-response relationships therefore involves a substantial element of scientific judgement. The considerations for developing or selecting a risk model appropriate for low dose extrapolation include: biologic plausibility, sensitivity to the shape of the observed dose-response relationship, the degree of linearity in the low dose region, interpretability of the estimated parameters, and flexibility to take account of survival variation. The relative importance of these considerations depends on the specific data sets available.

The use of mechanistic models rather than tolerance distribution models reflects an effort to utilize as fully as possible the current knowledge on carcinogenic processes. From this point of view, the staff of DHS considers the probit and logistic models the least appropriate choices for low dose extrapolation, and the mechanistic models the most biologically plausible.

Because the staff of DHS attempts to provide health conservative estimates of low dose risk, we frequently rely on the multistage model. This is because 1) it is somewhat more flexible than the one-hit, 2) it can fit a variety of empirical data sets reasonably well, 3) it has a plausible biological basis, and 4) it has the advantage over other mechanistic models of being essentially linear at low doses.

Appendix C

Mortality Among a Cohort of U.S. Cadmium Production Workers—an Update [1]

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ABSTRACT—A previous retrospective mortality study of 292 U.S. cadmium production workers employed for a minimum of 2 years showed increased mortality from respiratory and prostate cancer and from nonmalignant lung disease. To examine further the mortality experience of these workers, investigators from the National Institute for Occupational Safety and Health extended the study to include 602 white males with at least 6 months of production work in the same plant between 1940 and 1969. Vital status was determined through 1978, which included the addition of 5 years to the original follow-up. Cause-specific mortality rates for seven causes of death potentially related to cadmium exposure were compared between the overall cohort and U.S. white males and between subgroups. Mortality from respiratory cancer and from nonmalignant gastrointestinal disease was significantly greater among the cadmium workers than would have been expected from U.S. rates. All deaths from lung cancer occurred among workers employed for 2 or more years. A statistically significant dose-response relationship was observed between lung cancer mortality and cumulative exposure to cadmium. A 50% increase in lung cancer mortality, which was not statistically significant, was observed even among workers whose cumulative exposure to cadmium was between 41 and 200 $\mu g/m^3$ over 40 years. Since the previous investigation, no new deaths from prostate cancer and no excess of deaths from nonmalignant respiratory disease have been observed.—JNCI 1985; 74:325-333.

In 1976, Lemen et al. (*1*) published the results of a study on cancer mortality among cadmium production workers at a U.S. cadmium recovery plant. Using national white male rates for comparison, Lemen et al. reported a statistically significant excess of deaths from respiratory cancer (Obs=12; SMR=235), from nonmalignant respiratory disease (Obs=8; SMR=159), and, among workers with 20 or more years since first employment, from prostate cancer (Obs=4; SMR=452). The Lemen study included only hourly workers employed for 2 or more years between January 1, 1940, and December 31, 1969, and followed these workers through 1973.

A number of previous epidemiologic and experimental studies had suggested that cadmium might cause cancer of the prostate. Two occupational reports (*2, 3*) described excess mortality from prostate cancer among cadmium workers at a small British alkaline battery plant. Cadmium, like zinc, is known to concentrate in the prostate gland (*4-5*). Numerous toxicologic studies (*6-13*) have shown that injection of cadmium metal or salts into laboratory rats produces sarcomas locally and more distant interstitial cell tumors of the testes. On the basis of these findings, the IARC (*14*) concluded in 1976 that "occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man." Substantial controversy continues, however, and although several subsequent epidemiologic studies (*15-18*) have found increased mortality from prostate cancer among occupational groups, other studies (*19-21*) have not.

Still more controversial is the possible relationship between cadmium and lung cancer. At the time of the IARC working committee, only the Lemen et al. (*1*) study had found excess mortality from respiratory cancer. Interpretation of that study was complicated because some of the long-term workers in the cohort also had been exposed to arsenic during the 1920's when the plant functioned as an arsenic smelter. Concern about the potential carcinogenicity of cadmium to the lung has increased, however, due to recent animal data. Takenaka et al. (*22*) exposed rats continuously to cadmium chloride aerosol and found a dose-dependent increase in lung tumors at exposure levels well within the current occupational limit.

Because of continuing concern about the effects of chronic cadmium exposure on mortality, NIOSH has extended the follow-up of the cohort first described by Lemen et al. (*1*). The present report describes the mortality experience of the group through 5 additional years of observation, ending December 31, 1978. In

ABBREVIATIONS USED: CI=confidence interval; Exp=expected; HIS=Health Interview Survey; IARC=International Agency for Research on Cancer; ICD=International Classification of Disease; NIOSH=National Institute for Occupational Safety and Health; NMGID=nonmalignant gastrointestinal disease; Obs=observed; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; PY=person-years; PYAR=PY at risk of dying; SMR=standardized mortality ratio(s); SRR=standardized rate ratio(s); TWA=time-weighted average.

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[3] We thank Dr. George Hutchison, Dr. Karl Shy, and Dr. Philip Enterline for their advice in the analysis and interpretation of the data, Dr. Thomas Smith for his guidance in estimating exposures, and Dr. Lynne Moody for her epidemiologic and editorial counsel. We also acknowledge the dedicated follow-up efforts of Mrs. Edith Dodd, Mrs. Clorinda Battaglia, Ms. Judy Edelbrock, Ms. Mary Hogan, and their staffs and the excellent assistance in manuscript preparation by Ms. Fran Guerra.

addition, to allow for internal comparisons, the study population was expanded to include 257 workers with brief (6–23 mo) employment and more complete ascertainment of workers with 2 or more years of employment. The total study population includes 602 white males.

BACKGROUND

The industrial plant under study has refined cadmium metals and cadmium compounds since 1925. It functioned previously as an arsenic smelter from 1918 to 1925 and as a lead smelter from 1886 to 1918. Although some cadmium processing operations were begun prior to 1925, *the primary function of the plant for more than 50* years has been to recover cadmium and a number of other trace metals from "bag house" dust, a by-product of lead smelting. The facility is unusual in having a prolonged period of operation, with workers exposed predominantly to cadmium.

The industrial process recently was described by Smith et al. (*23*). Cadmium enters production principally as cadmium oxide dust (agglomerated fume). In a series of 10 physically isolated work areas, it is roasted, mixed with acid to form a cake, calcined, dissolved in water, recovered electrolytically, and treated further to produce cadmium oxide, metal, or yellow cadmium pigment. Air-monitoring data collected by the company from the 1940's to the present show that exposures differ substantially among departments and over time. Exposures have decreased over time due to the introduction of ventilation controls and to a mandatory respirator program introduced in the 1940's. Smith et al. (*23*) estimated the inhalation exposures that occurred in various departments (table 1). These estimates were based upon historical area monitoring data, adjusted to reflect the actual exposures of workers wearing respirators (*24*). Area-sampling data were first adjusted to reflect personal sampling, based on the ratio between area samples and personal exposure measurements from 1973 to 1976. For those departments and calendar periods in which workers wore respirators, the estimates of personal exposure were divided by 3.9, the geometric mean respirator protection factor measured in a survey at this plant in 1976 (*24*).

Also reflecting exposure are measurements of urine cadmium which the company obtained periodically on production workers since 1948. Urine samples were analyzed by colorimetric extraction until 1966 and subsequently by atomic absorption spectroscopy. Company records contained urine cadmium measurements for 261 members (43%) of the present cohort. These data are absent or extremely sparse for workers who left employment before 1960 and are representative only of production workers employed beyond 1960. Text-figure 1 shows the distribution of the median urine cadmium levels. These urine levels suggest a highly exposed population. They provide an index of group exposure but cannot be used to measure individual exposure because of the small number of samples for most workers (median of 2 *samples/person*; *range*, 0–79).

Few data are available on exposures other than cadmium at the smelter. Small quantities of high-purity lead, arsenic, thallium, and indium are produced sporadically by a few individuals in separate buildings. Some arsenic is evolved during cadmium recovery. An industrial hygiene survey conducted by NIOSH in 1973 found 0.3 and 1.1 μg arsenic/m^3 in the pre-melt department and 1.4 μg arsenic/m^3 in the retort department (*1*). These levels are substantially below the current OSHA 10 μg/m^3 PEL time-weighted average.

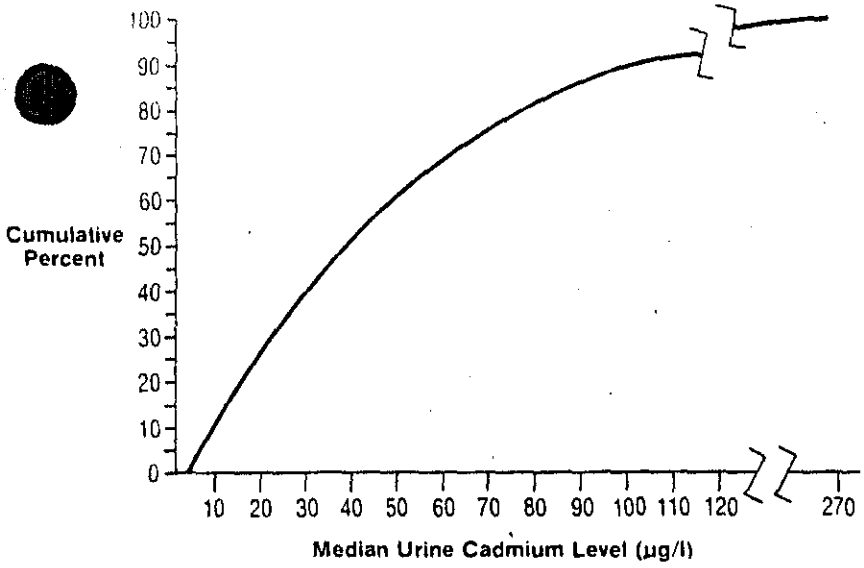
METHODS

The study population was defined from employment histories as recorded in the company personnel files. These records consist of a card for each employee and show the name, date of birth, social security number (since 1937), date of employment, date(s) of interruption of employment, and, in most cases, department or general work area for each period of employment. The records included retired and deceased as well as active employees. We enumerated all hourly employees and foremen who had worked a minimum of 6 months in a production area of the plant between January 1, 1940, and December 31, 1969. The requirement of production-area employment excluded several guards, office workers, and office area janitors who had been included in the Lemen et al. study (*1*). We also included production area foremen and a number of laborers whose records had been missing or whose employment histories had been inaccurately recorded and who thus had been omitted

TABLE 1.—*Estimates of cadmium inhalation exposures, by plant department and time period*[a]

Time period	Cadmium inhalation exposure, mg/m^3, in:									
	Plant departments:									Offices[c] and laboratories
	Sampling	Roaster	Mixing	Calcine	Solution	Tank house[b]	Foundry	Retort	Pigment	
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950–54	0.6	0.6	0.4	1.5	0.8	0.01	0.1	0.2	0.2	0.01
1955–59	0.6	0.6	0.4	1.5	0.4	0.01	0.1	0.2	0.04	0.01
1960–64	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.01	0.007
1965–76	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.01	0.007

[a] Data from Smith et al. (*24*).
[b] Tank house estimates also were used for nonproduction plant departments that were not measured directly, e.g., the repair shops.
[c] Office estimates also were used for nonplant areas that were not measured directly, e.g., areas patrolled by the plant guard.



TEXT-FIGURE 1.—Cumulative distribution of median urine cadmium levels among 261 members of the cohort with at least one urine cadmium measurement. The median urine cadmium, in micrograms/liter, was computed for each worker for whom urine samples were available.

from the Lemen cohort. NIOSH identified the cohort jointly with a representative from the company and reviewed the list with senior union officials.

For each worker, cumulative exposure to cadmium was calculated according to length of employment and jobs within the plant. Because many of the personnel records specified general work categories rather than single departments, we categorized each period of a worker's employment into one of 7 broad job categories; e.g., category 1 included production work in any of 6 "high"-exposure departments, including sampling, roasting and bag house, mixing, calcine, foundry, and retort. Category 2 included production work in the solution, tank house, and pigment departments. The average exposure to airborne cadmium for each of these composite categories was calculated on the basis of the industrial hygiene data in table 1 (*23*), with each department contributing to a weighted average according to the proportion of workers usually employed there. Each worker's cumulative exposure over time was computed as the sum of the number of days worked in a given job category multiplied by the average inhalation exposure of that category for the relevant time period. Cumulative exposure was expressed in milligram days per cubic meter (mg-days/m^3).

The vital status of all workers in the cohort was determined as of December 31, 1978. Follow-up procedures used the records of the Social Security Administration, of the state vital statistics offices, and of the company and union and direct telephoning. Death certificates were obtained for persons known to be deceased and were coded by a qualified nosologist according to the protocol of the ICD revision in effect at the time of death. The codes were subsequently converted to the seventh revision codes for the analysis (*25*). Under the rules of this and subsequent revisions, cancer is coded as the underlying cause of death if the immediate cause of death is "unmistakably a direct sequel of" the malignant disease. Deceased workers for whom no death certificate has yet been located were assumed dead on the date specified by the reporting agency, with cause of death unknown. Persons lost to follow-up were assumed to be alive—which might possibly result in overestimation of cause-specific expected deaths.

The mortality experience of the cohort was analyzed with the use of a modified life-table system developed by NIOSH (*25*). In this system, a worker accumulates PYAR upon completion of the eligibility period (in this study, at 6 months of employment). The PYAR are specific for 5-year age groups, calendar periods, and years since first employment (latency). An expected number of deaths is calculated by multiplying U.S. white male death rates by the corresponding age and calendar-year PYAR categories. The resulting quantities are summed over all ages and years to obtain the total expected numbers. The observed numbers of cause-specific deaths are compared with the numbers expected. The ratio of observed-to-expected deaths multiplied by 100 is expressed as the SMR.

In the initial analysis, in which mortality in the cadmium workers was compared to that of the general U.S. white male population, the causes for which excess mortality or morbidity were observed in previous studies of cadmium workers were considered a priori to be of particular interest. Those of central concern included deaths from prostate and lung cancers (*1, 20*) and from nonmalignant respiratory and renal diseases (*6, 15, 16*). Other conditions for which a priori concern has been raised include hypertension (*6, 26*) and renal cancer (*27*). Mortality from NMGID also was examined because of the acute gastrointestinal toxicity of cadmium and because of reports of chronic gastritis and gastrointestinal ulceration (*28–30*). Although in each case cadmium is suspected of causing an excess of mortality, we present 95% CI, corresponding to a two-sided alpha level of 0.05, throughout this paper. Where the 95% CI includes the null but the 90% does not, we present both. CI were

TABLE 2.—*Vital status of white male cadmium production workers, by employment duration*

Worker status	Workers, No. (%) employed		
	6–23 mo	2+ yr	Total
Alive	189 (74)	222 (64)	411 (69)
Dead	60 (23)	119 (35)	179 (29)
Lost to follow-up	8 (3)	4 (1)	12 (2)
Total	257	345	602

calculated with the use of Fisher's exact CI (if either the observed or expected was less than 10) or approximate CI (if observed or expected frequencies were 10 or more) (*31*).

For selected causes of death we examined mortality in relation to cumulative exposure to cadmium. For subgroup comparisons we used the directly standardized SRR as the measure of effect (*32*). To compute these, the age-specific and calendar time-specific rates of the subgroup were multiplied by the corresponding PYAR cells of the standard population—here the PYAR distribution of the overall cadmium cohort. The results were summed to yield the expected number of deaths that would occur in the overall cohort were the rates of the subgroup to apply. This total number of expected deaths was divided by the total number of PYAR in the overall cohort to yield a directly standardized mortality rate. The ratio of this rate to the standardized rate for the overall cohort, if U.S. age, sex, race, and calendar-period rates applied, yielded the SRR.

To analyze mortality by cumulative exposure, we chose the exposure categories a priori, on the basis of current or proposed regulatory standards and on the assumption that such standards are intended to protect a worker over a 40-year working lifetime; e.g., 40 years' exposure to cadmium at or below the current NIOSH proposed TWA of 40 $\mu g/m^3$ would result in a cumulative exposure of up to 584 mg-days/m^3. Forty years' exposure to cadmium at levels above the current NIOSH TWA, but within the current OSHA 200 $\mu g/m^3$ PEL, would result in a cumulative exposure of up to 2,920 mg-days/m^3.

RESULTS

Because of the small number of nonwhites and females (total=13) in the cohort, we restricted the analysis to the 602 white males. Table 2 shows the vital status of these workers, by duration of employment, as of December 31, 1978. Of these, 411 were alive, 179 were dead, and 12 (2.0%) had unknown vital status; 43% had been employed for less than 2 years.

Text-figure 2 shows the distribution of the cohort by year of first employment. Two-thirds of the individuals had started work before 1949 and thus could be followed beyond 30 years. Nearly 83% had over 20 years of follow-up.

Table 3 compares the number of cause-specific deaths among the overall cohort with the number expected, based on U.S. rates. A deficit was observed in mortality from all causes (SMR=95; 95% CI=81–110), due to a deficit in diseases of the circulatory system (SMR=65; 95% CI=49–85). Significantly increased mortality was observed for respiratory cancer and NMGID. The excess of nonmalignant respiratory disease was not statistically significant in the overall cohort.

Twenty deaths were due to respiratory cancer, all among workers with over 2 years' employment and all due to cancers of the lung, trachea, and bronchus. Expected deaths were 11.43 in this more specific subgroup (ICD code 162–163), which was subsequently called lung cancer. Two of the deaths from lung cancer were initially miscoded as being due to other causes. Inasmuch as the immediate causes of these 2 deaths were unmistakably direct sequels of malignant conditions, the deaths were recoded to lung cancer in accordance with the rules of the ICD Seventh Revision. Analysis that excluded these cases yielded an SMR for lung cancer of 157 (18 Obs vs. 11.43 Exp; 95% CI=93–249; 90% CI=102–234).

TEXT-FIGURE 2.—Cumulative distribution by year of first employment for cadmium production workers included in cohort.

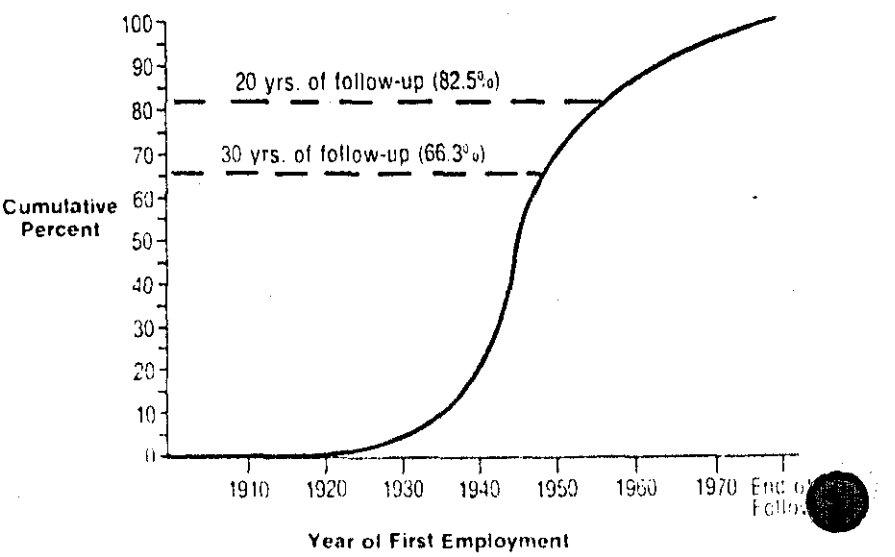


TABLE 3.—*Mortality from selected causes of death among white males with 6 or more months of cadmium production work: 1940–69*

Cause of death	ICD, 7th revision	No. of deaths		SMR	95% CI
		Obs	Exp		
Malignant neoplasm	140–199	41	36.46	112	81–153
Digestive system	150–159	7	10.85	65	26–133
Respiratory system	160–164	20	12.15	165	101–254
Genitourinary tract	177–182	6	4.45	135	49–293
Lymphatic and hematopoietic tissues	200–205	3	3.37	89	17–270
Other unspecified neoplasms		5	5.64	89	29–207
Diseases of the circulatory system: Heart disease	400–468	56	85.68	65	49–85
Nonmalignant respiratory diseases	470–493, 500–527	16	10.37	154	88–251
Acute infections, influenza, pneumonia	470–493	7	4.47	157	63–323
Other respiratory diseases	500–527	9	5.90	153	69–290
NMGID	540–543, 560–561, 570	9	2.35	383	175–727
All other causes	—	57	54.01	106	80–137
All causes of death	—	179	188.87	95	81–110

Of the 6 deaths from genitourinary cancer, 1 was due to renal cancer (vs. 0.92 Exp), 2 to cancers of the bladder and other urinary organs (vs. 1.10 Exp), and 3 to prostate cancer (vs. 2.20 Exp). No new deaths from prostate cancer were observed since the Lemen et al. report (*1*).

One of the original prostate cases was a plant guard who was excluded from this cohort because he had not worked 6 months in a production area. Another deceased worker had prostate cancer listed as a contributing cause of death but could not be included in this analysis because prostate cancer was not listed as the underlying cause of death. The remaining 3 deaths from prostate cancer had occurred among workers with 2 or more years of employment and 20 or more years of observation (vs. 1.41 Exp; SMR=213; 95% CI=44–622).

Sixteen deaths occurred due to nonmalignant respiratory disease; 7 of these involved workers employed for less than 2 years. The death certificates of 3 workers mentioned silicosis. Silica exposure may have occurred from work with refractory brick in furnace areas of the plant but is undocumented. One of the workers whose certificate mentioned advanced silicosis had been employed for only 1 year, suggesting that the exposure had occurred elsewhere.

We noted 9 deaths from NMGID, excluding cirrhosis. The death certificates of 6 of these suggested peptic ulcer disease. Most of the deaths from NMGID were of long-term employees, whereas 5 of the 6 deaths attributed to cirrhosis involved short-term workers.

No excesses were noted for deaths attributable to hypertension (3 Obs; 3.22 Exp) or to nonmalignant renal disease (1 Obs; 1.35 Exp). A single death certificate listed renal disease as the underlying cause of death [death had been due to acute nephritis (ICD code 590)], and 4 other certificates listed nonmalignant renal disease as a contributing cause of death. No comparison rates were available for analysis of these contributing causes of death.

Arsenic Exposure

Substantial arsenic exposure occurred throughout the plant during the years 1918–25 when the facility functioned as an arsenic smelter. Because arsenic is a known risk factor for lung cancer (*33*), we stratified the cohort into workers employed before and those first employed on or after January 1, 1926. We then compared mortality from lung cancer among each of these subgroups with that of U.S. white males (table 4). Lung cancer mortality was significantly elevated among persons hired prior to January 1, 1926. Among workers hired after that date, the excess of lung cancer deaths was statistically significant among workers employed for 2 or more years. When the 2 initially miscoded deaths from lung cancer are excluded from this analysis, mortality from lung cancer remains statistically above that expected both for workers hired prior to 1926 (Obs=3; Exp=0.56; 95% CI=110–1565) and for workers with 2 or more years' employment who had been hired after 1926 (Obs=15; Exp=7.0; 95% CI=120–353).

Mortality by Cumulative Exposure to Cadmium

Tables 5 and 6 present data on mortality from lung cancer and NMGID in relation to cumulative exposure to

TABLE 4.—*Mortality from lung cancer (ICD 162–163) in white male cadmium production workers, by date of hire*

Worker employment status	No. of deaths		SMR	95% CI
	Obs	Exp		
Hired prior to January 1, 1926	4	0.56	714	195–1829
Hired on or after January 1, 1926				
Overall cohort	16	10.87	147	84–239
≥2 years employment	16	7.00	229	131–371

cadmium. Only the 576 workers hired on or after January 1, 1926, are included in these analyses. Lung cancer mortality increased with increasing cumulative exposure to cadmium, and this trend was apparent both in the SRR and the SMR. A similar pattern was seen when the analysis was restricted to workers with 20 or more years since first exposure. The regression slope for the SRR for lung cancer (table 5) was 7.33×10^{-7} ($P=.0001$). The excess of deaths from lung cancer was statistically significant only for the stratum of workers whose cumulative exposure to cadmium exceeded 2,920 mg-days/m^3, the level corresponding to a 40-year exposure above the current OSHA limit (95% CI for the SMR = 113–577). In a separate analysis (not shown), workers whose cumulative exposure to cadmium ranged from 293 to 584 mg-days/m^3 showed an SMR for lung cancer of 100 and an SRR of 0.96. This level of cumulative exposure is equivalent to 10 years' exposure to airborne cadmium at levels between 21 and 40 μg/m^3. In contrast to its relationship with cumulative exposure, the excess of lung cancer mortality did not increase with length of employment beyond 2 years. Workers employed for 2–9 years, 10–19 years, and 20 or more years all showed approximately twice the number of deaths from lung cancer as expected from the U.S. rates.

Only 6 deaths from NMGID occurred among workers hired since 1926. A statistically significant upward trend was evident in the SRR when mortality from NMGID was analyzed by cumulative exposure (slope $=2.73\times10^{-7}$; $P=.014$). Because of the small number of cases of NMGID, these estimates are less stable than those for lung cancer. Three additional deaths from NMGID occurred among the 26 workers hired before 1926. If arsenic were unrelated to NMGID, these deaths would increase further the observed mortality in the high-exposure, long-term employment subgroup.

A similar analysis of deaths from nonmalignant respiratory disease was not performed, inasmuch as this study found no significant excess of deaths from this cause either in the overall cohort or among workers with 2 or more years of employment. An excess of deaths in this category was apparent, however, among workers employed for 6 months to 2 years (Obs = 8; Exp = 3.2; SMR = 249; 95% CI = 108–491). One of these deaths was attributable to silicosis.

TABLE 5.—*Lung cancer (ICD 162–164) mortality, by cumulative exposure to cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent[a]	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7,005	2	53	0.48
585–2,920[b]	41–200 μg/m^3	5,825	7	152	1.55
≥2,921	≥200 μg/m^3	2,214	7	280	3.45
U.S. white males		—	—	100	1.00

[a] The TWA that over a 40-year working lifetime would result in the indicated cumulative exposure.

[b] Exclusion of the single worker hired after 1926, whose death from lung cancer was initially miscoded, reduces the number of observed deaths in this stratum to 6 and the SRR to 1.31.

TABLE 6.—*NMGID (ICD 530.4, 560.81, and 570) mortality, by cumulative exposure to airborne cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent[a]	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7,005	2	300	1.8
585–2,920	41–200 μg/m^3	5,825	1	112	1.0
≥2,921	≥200 μg/m^3	2,214	3	582	11.3
U.S. white males		—	—	100	1.00

[a] The TWA that over a 40-yr working lifetime would result in the indicated cumulative exposure.

DISCUSSION

The findings of principal interest in this study were the increased mortality from lung cancer among workers employed for 2 or more years and the dose-response relationship between lung cancer mortality and cumulative exposure to cadmium. The excess of malignant respiratory disease, noted previously in this cohort by Lemen et al. (*1*), has continued during the expanded observation period. Eight new deaths from lung cancer have been identified. The excess of deaths from respiratory cancer among workers with 2 or more years of employment continues to be statistically significant (Obs = cases = 8; Exp = 2.94; SMR = 272; 95% CI = 117–536). Furthermore, because national death rates for respiratory cancer overestimate regional (State of Colorado and Denver County) rates by 10–25% (*34*), the measured excess of lung cancer deaths among longer-term employees probably underestimates the actual increase.

The observed excess of deaths from respiratory cancer could be due to a true causal relationship between cadmium and lung cancer, to bias (the effect of uncontrolled confounding), or to chance. Cigarette smoking and exposure to arsenic are two extraneous factors which, if uncontrolled in the analysis, could explain the findings. Although the tobacco smoking habits of these cadmium workers were not recorded at the time of employment, company representatives did collect information on past tobacco use by mailing a questionnaire to members of the cohort in 1982 (*35*). Interviews with approximately 70% of survivors or next of kin showed that 77.5% of those for whom information was gathered were current or former smokers. This prevalence of "ever smokers" resembles the 72.9% prevalence noted among U.S. white males, age 20 or over, in the 1965 HIS (*36*). The 1965 HIS is perhaps the best source of information on the smoking habits of the general population during the observation period of this study. Using the 1965 survey data, one can estimate the effect that disproportionately heavy smoking by the cadmium workers would have on lung cancer mortality relative to that of the general population. Computations developed by [illegible] (*37*) and Blair and Spiritas (*38*), combined with the HIS

data, show that even an assumed doubling of the proportion of heavy smokers will have only a small effect on the rate ratio for lung cancer; e.g., if 40% of the cadmium workers smoked more than 25 cigarettes/day, compared to 20% of the 1965 white male general population, the rate ratio would increase only 1.25-fold. Thus cigarette smoking alone is unlikely to account for the twofold-to-threefold increase in deaths from lung cancer observed among workers in this cohort who had had 2 or more years of employment.

Substantial and widespread arsenic exposure occurred prior to 1926 when the plant operated as an arsenic smelter. The rate of lung cancer mortality among the 26 workers employed before 1926 was nearly six times the U.S. rates. Even after 1925, a small and unspecified number of workers occasionally processed arsenic in one area of the plant. This was an intermittent operation, apparently staffed by workers from the roasting area, and lasted into the 1930's. A second and continuing source of exposure involved workers in the sampling, mixing, roasting, and calcine furnace areas of the plant who were exposed to arsenic contamination from the incoming feed material. Only six industrial hygiene measurements were made in these areas before 1975. In 1950, airborne arsenic concentrations ranged from 300 to 700 $\mu g/m^3$ near the roasting and calcine furnaces, the areas of highest exposure. Measurements by the company and OSHA in 1979 show that arsenic exposures in these areas had decreased to about 100 $\mu g/m^3$. Although air levels of arsenic in this confined area were still 10 times higher than the legal OSHA threshold limit value of 10 $\mu g/m^3$, actual personal exposures were lower due to respirator usage. One can estimate the number of lung cancer deaths potentially attributable to arsenic by assuming *a*) an average airborne arsenic exposure of 500 $\mu g/m^3$ in the "high-arsenic" work areas during the years of this study, *b*) a respirator protection factor of 75% (similar to that assumed for cadmium), and *c*) an estimated 20% of PY of exposure spent in high-arsenic jobs, an estimate based on personnel and biologic monitoring data. On the basis of these assumptions, the average airborne arsenic exposure of persons in this study would have been 25 $\mu g/m^3$. Inasmuch as the 576 workers hired after 1926 were employed an average of 3 years, they acquired 1,728 PY of exposure to 25 $\mu g/m^3$. Such an exposure should result in no more than 0.77 lung cancers, on the basis of a risk assessment model for arsenic developed by the OSHA (*39*).

Although the estimate of an average air exposure to arsenic of 25 $\mu g/m^3$ rests on several assumptions, it is more likely to overestimate than to underestimate actual exposures. Only a fraction of jobs in the high-arsenic areas involved exposures as high as those of the furnace areas. High-exposure jobs in the roaster area were frequently staffed by entry-level workers, many of whom worked less than 6 months. These very short-term workers with brief but high exposure were excluded from the mortality study, yet they were included in our estimate of 20% of PY of exposure spent in high-arsenic jobs. In addition, urinary arsenic levels measured on workers in the high arsenic areas from 1960 to 1980 averaged only 16 μg/liter, a level consistent with an average inhaled arsenic concentration of 14 $\mu g/m^3$ (*40*). Thus the assumption of an average inhaled concentration of 125 $\mu g/m^3$ (25% of 500 $\mu g/m^3$) over these years overestimates the actual exposures by ninefold, more than compensating for the unquantified higher exposures during the early years. Arsenic alone does not appear to explain the observed excess of deaths from lung cancer.

The central finding of the study was the observed dose-response relationship between mortality from lung cancer and cumulative exposure to cadmium. Previous epidemiologic studies of cadmium workers have had insufficient industrial hygiene data to estimate cumulative exposure. The strong dose-response pattern observed in this study is consistent with a causal relationship between cadmium and lung cancer. It also suggests that the current OSHA occupational standard, limiting exposure to cadmium dust to 200 $\mu g/m^3$, is inadequate to protect workers over a 40-year working lifetime. Workers whose cumulative exposure was below the 40-year equivalent of the NIOSH-recommended TWA of 40 $\mu g/m^3$ showed no excess of lung cancer deaths, whereas workers whose cumulative exposure was within the current OSHA limit but above the NIOSH recommended limit showed a 50% excess in lung cancer deaths.

The potential role of cadmium as a pulmonary carcinogen has gained biologic plausibility because of the experimental induction of lung cancer in rats exposed to cadmium chloride aerosol (*22*). Epidemiologic studies of mortality among cadmium workers in England and Sweden have, however, shown conflicting results. Sorahan and Waterhouse (*18*) found a statistically significant excess of deaths from respiratory cancer (Obs=89; Exp=70.2; SMR=127; 90% CI=106-151) in a cohort of 3,025 English nickel-cadmium battery workers. A subset of these workers had been included in the earlier studies of Potts (*2*) and Kipling and Waterhouse (*3*). Although the authors observed a positive association between death from respiratory cancer and cumulative duration of employment in jobs with high or moderate exposure to cadmium, they noted that these workers also were exposed potentially to oxyacetylene welding fumes and to nickel hydroxide dust. Holden (*17*) found a statistically significant excess of deaths from respiratory cancer (Obs=36; Exp=26.06; SMR=138; 95% CI=108-339) and from prostate cancer (Obs=8; Exp=3.00; SMR=267; 90% CI=115-525) among 624 cadmium "vicinity" workers but not among 347 workers employed directly in manufacturing cadmium copper alloys. The vicinity workers were also exposed to arsenic.

Armstrong and Kazantzis (*19*), excluding the cohorts studied by Sorahan and Waterhouse (*18*) and Holden (*17*), recently described mortality among workers enrolled in the registry of English cadmium workers. A small, statistically insignificant excess of deaths from respiratory cancer was evident in the overall cohort (Obs=199; Exp=185.6; SMR=107; 95% CI=92-122). This marginal excess is consistent with the results in our study, inasmuch as most of the workers in the Armstrong cohort

had only minimal exposure to cadmium. Less than 3% of the workers in the Armstrong cohort were classified as "ever highly exposed." High exposure was defined as having worked at least 1 year in a job that the authors judged would produce a urine cadmium level of at least 20 μg liter following chronic exposure. In our cohort, 81% of workers for whom urine cadmium had been measured had a median urine cadmium of at least 20 μg/liter. Even among workers with less than 2 years of employment, approximately 30% had a median urine level of 20 μg/liter. One might argue that in each of the epidemiologic studies in which excess mortality from lung cancer was seen, other occupational exposures such as arsenic or nickel were present and could have contributed to the problem. Unfortunately, the published versions of these studies do not include sufficient information on the level of exposure to either cadmium or to other metals to permit assessment of this problem.

Increased mortality from NMGID has not been reported previously in association with cadmium. Ingested cadmium is a severe gastrointestinal irritant in man (*5*, *28*), and Tsuji et al. (*29*) and Adams et al. (*30*) have commented on the frequent observation of gastritis and gastrointestinal ulceration among chronically exposed persons. In our study we observed a 2.8-fold overall increase in deaths from NMGID (excluding cirrhosis of the liver) among workers employed on or after January 1, 1926. Deaths from these causes showed a general association with prolonged employment. Because NMGID previously has not been examined systematically, we view this finding as a hypothesis to be examined further in future studies rather than as a definitive conclusion.

No new deaths from prostate cancer have occurred in this cohort since the Lemen study (*1*). In addition, 1 of the 4 original cases was excluded from this analysis because of the revised definition of the cohort. The excluded worker had been employed for 13 years as a guard who patrolled the entire plant but at no time had worked for 6 months in a production area. Exclusion of such a worker is to a certain extent arbitrary. Also, because the small size and short additional follow-up of this cohort has low statistical power, and because prostate cancer is frequently a nonfatal disease imperfectly studied by death certificate data, we believe that the absence of new cases during the 5 additional years of follow-up weakens but does not refute the possible association between cadmium and prostate cancer.

The presence of only 1 death attributed to chronic renal failure is interesting, inasmuch as cadmium is a known nephrotoxin and because increased mortality from chronic nephritis and nephrosis has been noted among Swedish battery workers (*15*, *16*). The difference may well be due to local differences in recording certain types of information on death certificates. The comparisons in our study were based upon the underlying causes of death and ignore the data for 4 individuals for whom renal disease was noted as a contributing cause of death. Impaired renal function frequently is underreported on death certificates, even when the disease was sufficiently severe to require chronic hemodialysis (*41*).

In contrast to the Lemen study (*1*), we found no excess of deaths from nonmalignant respiratory disease either in the overall cohort or among workers with 2 or more years of employment. If deaths from silicosis are excluded, the only increase in mortality from these causes is among workers with short-term employment. The significance of this finding is unclear.

In summary, the finding of increased lung cancer mortality in this follow-up analysis is consistent 1) with the previous mortality study of this cohort (*1*), 2) with the recently published rat inhalation study (*13*), and 3) with the epidemiologic findings of Sorahan and Waterhouse (*18*). An association of cadmium with NMGID was also observed. Previous findings (*1–3*) of prostate cancer among exposed workers were somewhat weakened.

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Appendix D

The construction of life tables is described in detail by Chiang (1984). The abridged life table uses age intervals larger than one year (in this case, five-year age intervals). The data collected from vital statistics are:

m_i = annual death rate for age interval i

ℓ_i = annual lung cancer death rate for age interval i

The life table is constructed by calculating the following:

(1) The probability of dying in the i^{th} age interval, given survival to the beginning of that interval:

$$q_i = 1-\exp(-5 \cdot m_i)$$

(2) The probability of surviving the i^{th} age interval, given survival to the beginning of that interval:

$$p_i = 1-q_i$$

(3) The cumulative probability of surviving to the beginning of the i^{th} age interval:

$$c_i = p_1 \cdot p_2 \cdots p_{i-1} = \prod_{j=1}^{i-1} p_j$$

(4) The probability of dying of lung cancer in the i^{th} interval, given survival to the beginning of that interval:

$$p\ell_i = (\ell_i/m_i) \cdot q_i$$

(5) The unconditional probability of dying of lung cancer in the i^{th} interval, (i.e. not conditioned on surviving to the beginning of the interval) is

$$p\ell_i \cdot c_i$$

(6) The cumulative probability of dying of lung cancer through the end of the i^{th} interval:

$$c\ell_i = p\ell_1 c_1 + p\ell_2 c_2 + \cdots + p\ell_i c_i = \sum_{j=1}^{i} p\ell_j c_j$$

The life table for an exposed population is constructed in an identical manner such that only the data for the age-specific lung cancer death rates are modified. (This also changes the age-specific overall death rates.) The lung cancer death rates (ℓ_i) for an exposed population are derived by adding the observed rates in an unexposed population to the excess rates predicted by the model. The overall death rates (m_i) are obtained by adding the observed nonlung cancer death rates to the predicted lung cancer death rates. From these values, a new life table is constructed.

The cumulative probability of a lung cancer death for the last age interval in an exposed population is then compared to the same probability in an unexposed population. The difference between the two is the excess lung cancer death rate due to exposure.

TABLE D-1a

LIFE TABLE FOR CALIF MALES
BACKGROUND : LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034568	0.982864	1.00000	0.000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98286	0.000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.000000	0.0000000	0.0000000	0.0000000
4	15	0.0015043	0.992358	0.97947	0.000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.000015	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.000036	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983481	0.93185	0.000214	0.0010611	0.0009888	0.0012286
10	45	0.0053525	0.973592	0.91646	0.000456	0.0022498	0.0020618	0.0032904
11	50	0.0082844	0.959424	0.89225	0.000933	0.0045697	0.0040773	0.0073677
12	55	0.0129352	0.937366	0.85605	0.001496	0.0072432	0.0062006	0.0135683
13	60	0.0199206	0.905197	0.80243	0.002312	0.0110029	0.0088291	0.0223974
14	65	0.0309841	0.856483	0.72636	0.003265	0.0151233	0.0109850	0.0333824
15	70	0.0466398	0.792036	0.62212	0.004359	0.0194407	0.0120944	0.0454768
16	75	0.0701389	0.704199	0.49274	0.004803	0.0202560	0.0099809	0.0554577

TABLE D-1b

LIFE TABLE FOR CALIF FEMALES
BACKGROUND : LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98659	0.000005	0.00002498	0.00002465	0.0000246
3	10	0.0002384	0.998809	0.98539	0.000000	0.00000000	0.00000000	0.0000246
4	15	0.0005583	0.997212	0.98422	0.000002	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.000002	0.00000998	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97845	0.000002	0.00000998	0.00000977	0.0000540
7	30	0.0008328	0.995845	0.97494	0.000015	0.00007484	0.00007297	0.0001270
8	35	0.0012411	0.993814	0.97033	0.000039	0.00019440	0.00018874	0.0003157
9	40	0.0020251	0.989925	0.96488	0.000113	0.00056215	0.00054241	0.0008582
10	45	0.0030578	0.984827	0.95516	0.000244	0.00121072	0.00115643	0.0020146
11	50	0.0048217	0.976180	0.94057	0.000462	0.00228238	0.00214695	0.0041615
12	55	0.0072160	0.964563	0.91826	0.000738	0.00362423	0.00332798	0.0074895
13	60	0.0112514	0.945296	0.88572	0.001011	0.00491544	0.00435370	0.0118432
14	65	0.0168356	0.919268	0.83727	0.001212	0.00581195	0.00486615	0.0167094
15	70	0.0263732	0.876458	0.76967	0.001305	0.00611309	0.00470507	0.0214144
16	75	0.0405130	0.816633	0.67459	0.001126	0.00509641	0.00343796	0.0248524

TABLE D-2a

LIFE TABLE FOR CALIF MALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034568	0.982864	1.00000	0.00000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98286	0.00000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.00000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.00000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.00000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.00000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.00001500	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.00003600	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983481	0.93185	0.00021401	0.0010612	0.0009888	0.0012286
10	45	0.0053525	0.973592	0.91646	0.00045601	0.0022498	0.0020619	0.0032905
11	50	0.0092845	0.959424	0.89225	0.00093303	0.0045699	0.0040775	0.0073680
12	55	0.0129363	0.937366	0.85605	0.00149605	0.0072435	0.0062008	0.0135688
13	60	0.0199207	0.905196	0.80243	0.00231209	0.0110034	0.0088295	0.0223982
14	65	0.0309842	0.856483	0.72636	0.00326514	0.0151239	0.0109854	0.0333836
15	70	0.0466300	0.792035	0.62211	0.00435920	0.0194416	0.0120949	0.0454785
16	75	0.0701392	0.704198	0.49274	0.00480323	0.0202570	0.0099813	0.0554599

TABLE D-2b

LIFE TABLE FOR CALIF FEMALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.00000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98658	0.00000500	0.00002499	0.00002465	0.0000246
3	10	0.0002384	0.998809	0.98539	0.00000000	0.00000000	0.00000000	0.0000246
4	15	0.0005584	0.997212	0.98422	0.00000200	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.00000200	0.00000998	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97846	0.00000200	0.00000998	0.00000977	0.0000540
7	30	0.0008328	0.995845	0.97494	0.00001500	0.00007485	0.00007297	0.0001270
8	35	0.0012411	0.993814	0.97093	0.00003900	0.00019440	0.00018874	0.0003158
9	40	0.0020251	0.989925	0.96483	0.00011300	0.00056216	0.00054242	0.0008582
10	45	0.0030578	0.984827	0.95516	0.00024401	0.00121076	0.00115646	0.0020146
11	50	0.0048217	0.976180	0.94057	0.00046202	0.00228245	0.00214702	0.0041617
12	55	0.0072160	0.964563	0.91826	0.00073803	0.00362436	0.00332809	0.0074898
13	60	0.0112515	0.945296	0.88572	0.00101104	0.00491563	0.00435386	0.0118436
14	65	0.0168356	0.919267	0.83727	0.00121205	0.00581219	0.00486635	0.0167100
15	70	0.0263733	0.876458	0.76967	0.00130506	0.00611336	0.00470528	0.0214152
16	75	0.0405131	0.816633	0.67458	0.00112605	0.00509665	0.00343812	0.0248534

TABLE D-3a

LIFE TABLE FOR CALIF MALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
UPPER CONFIDENCE LIMIT - LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034558	0.982854	1.00000	0.00000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98286	0.00000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.00000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.00000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.00000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.00000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.00001500	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.00003601	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983480	0.93185	0.00021404	0.0010613	0.0009890	0.0012288
10	45	0.0053526	0.973592	0.91646	0.00045609	0.0022502	0.0020622	0.0032911
11	50	0.0082847	0.959423	0.89225	0.00093321	0.0045708	0.0040783	0.0073693
12	55	0.0129356	0.937365	0.85609	0.00149638	0.0072450	0.0062021	0.0135714
13	60	0.0199212	0.905194	0.80243	0.00231263	0.0110059	0.0088315	0.0224029
14	65	0.0309850	0.856479	0.72635	0.00326597	0.0151277	0.0109881	0.0333911
15	70	0.0456312	0.792030	0.62211	0.00436038	0.0194469	0.0120980	0.0454891
16	75	0.0701406	0.704193	0.49273	0.00480463	0.0202628	0.0099840	0.0554731

TABLE D-3b

LIFE TABLE FOR CALIF FEMALES - CUMULATIVE DOSE - NO LAG
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
UPPER CONFIDENCE LIMIT - LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.986584	1.00000	0.00000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98659	0.00000500	0.00002499	0.00002465	0.0000247
3	10	0.0002384	0.998809	0.98539	0.00000000	0.00000000	0.00000000	0.0000247
4	15	0.0005584	0.997212	0.98422	0.00000200	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.00000200	0.00000999	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97846	0.00000200	0.00000998	0.00000977	0.0000540
7	30	0.0006328	0.995845	0.97494	0.00001500	0.00007485	0.00007298	0.0001270
8	35	0.0012411	0.993813	0.97088	0.00003901	0.00019443	0.00018877	0.0003158
9	40	0.0020252	0.989925	0.96489	0.00011302	0.00056225	0.00054251	0.0008583
10	45	0.0030579	0.984827	0.95516	0.00024405	0.00121097	0.00115667	0.0020150
11	50	0.0046218	0.976179	0.94066	0.00046211	0.00228290	0.00214745	0.0041624
12	55	0.0072162	0.964562	0.91826	0.00073819	0.00362514	0.00332881	0.0074912
13	60	0.0112517	0.945295	0.88572	0.00101128	0.00491678	0.00435488	0.0118461
14	65	0.0166359	0.919266	0.83726	0.00121236	0.00581366	0.00486757	0.0167137
15	70	0.0263737	0.876456	0.76967	0.00130541	0.00611502	0.00470654	0.0214202
16	75	0.0405134	0.816632	0.67458	0.00112638	0.00509813	0.00343910	0.0248593

TABLE D-4b

LIFE TABLE FOR CALIF FEMALES - 10 YR LAGGED CUMULATIVE DOSE
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0027014	0.926584	1.00000	0.00000000	0.00000000	0.00000000	0.0000000
2	5	0.0002418	0.998792	0.98658	0.00000500	0.00002498	0.00002465	0.0000246
3	10	0.0002384	0.998809	0.98537	0.00000000	0.00000000	0.00000000	0.0000246
4	15	0.0005584	0.997212	0.98422	0.00000200	0.00000999	0.00000983	0.0000345
5	20	0.0006160	0.996925	0.98147	0.00000200	0.00000998	0.00000980	0.0000443
6	25	0.0007208	0.996402	0.97846	0.00000200	0.00000998	0.00000977	0.0000540
7	30	0.0008228	0.995845	0.97494	0.00001500	0.00007485	0.00007297	0.0001270
8	35	0.0012411	0.993814	0.97089	0.00003900	0.00019440	0.00018874	0.0003158
9	40	0.0020251	0.989925	0.96483	0.00011300	0.00056216	0.00054242	0.0008582
10	45	0.0030578	0.984827	0.95516	0.00024401	0.00121075	0.00115646	0.0020146
11	50	0.0046217	0.976180	0.94057	0.00046201	0.00228244	0.00214701	0.0041616
12	55	0.0072160	0.964563	0.91826	0.00073802	0.00362433	0.00332807	0.0074897
13	60	0.0112515	0.945296	0.88572	0.00101103	0.00491560	0.00435384	0.0118435
14	65	0.0168356	0.919268	0.83727	0.00121204	0.00581216	0.00486632	0.0167099
15	70	0.0263733	0.876458	0.76967	0.00130505	0.00611333	0.00470525	0.0214151
16	75	0.0405130	0.816633	0.67458	0.00112605	0.00509662	0.00343810	0.0248532

TABLE D-4a

LIFE TABLE FOR CALIF MALES - 10 YR LAGGED CUMULATIVE DOSE
CONSTANT EXPOSURE AT 1 NG/CUBIC METER OF CADMIUM
LUNG CANCER DEATHS

OBS	AGE	ANNUAL DEATH RATE AGE INTERVAL I TO I+4	P(SURVIVAL TO I+4 GIVEN SURVIVAL TO I)	CUMULATIVE P(SURVIVAL TO AGE I)	ANNUAL LUNG CANCER DEATH RATE IN (I, I+4)	P(LUNG CANCER DEATH GIVEN SURVIVAL TO I)	UNCONDITIONAL P(LUNG CANCER DEATH)	CUMULATIVE P(LUNG CANCER DEATH BY I+4)
1	0	0.0034568	0.982864	1.00000	0.00000000	0.0000000	0.0000000	0.0000000
2	5	0.0003318	0.998342	0.98286	0.00000000	0.0000000	0.0000000	0.0000000
3	10	0.0003606	0.998199	0.98123	0.00000000	0.0000000	0.0000000	0.0000000
4	15	0.0015343	0.992358	0.97947	0.00000000	0.0000000	0.0000000	0.0000000
5	20	0.0020493	0.989806	0.97198	0.00000000	0.0000000	0.0000000	0.0000000
6	25	0.0020206	0.989948	0.96207	0.00000000	0.0000000	0.0000000	0.0000000
7	30	0.0020375	0.989864	0.95240	0.00001500	0.0000746	0.0000711	0.0000711
8	35	0.0023257	0.988439	0.94275	0.00003600	0.0001790	0.0001687	0.0002398
9	40	0.0033315	0.983481	0.93185	0.00021400	0.0010612	0.0009888	0.0012286
10	45	0.0053525	0.973392	0.91645	0.00045601	0.0022498	0.0020619	0.0032905
11	50	0.0082845	0.959424	0.89225	0.00093302	0.0045698	0.0040774	0.0073679
12	55	0.0129353	0.937366	0.85605	0.00149604	0.0072434	0.0062007	0.0135687
13	60	0.0199206	0.905197	0.80243	0.00231208	0.0110033	0.0088294	0.0223981
14	65	0.0309842	0.856483	0.72635	0.00326512	0.0151238	0.0109853	0.0333834
15	70	0.0466279	0.792035	0.62211	0.00435917	0.0194415	0.0120948	0.0454782
16	75	0.0701391	0.704198	0.49274	0.00480320	0.0202568	0.0099813	0.0554595