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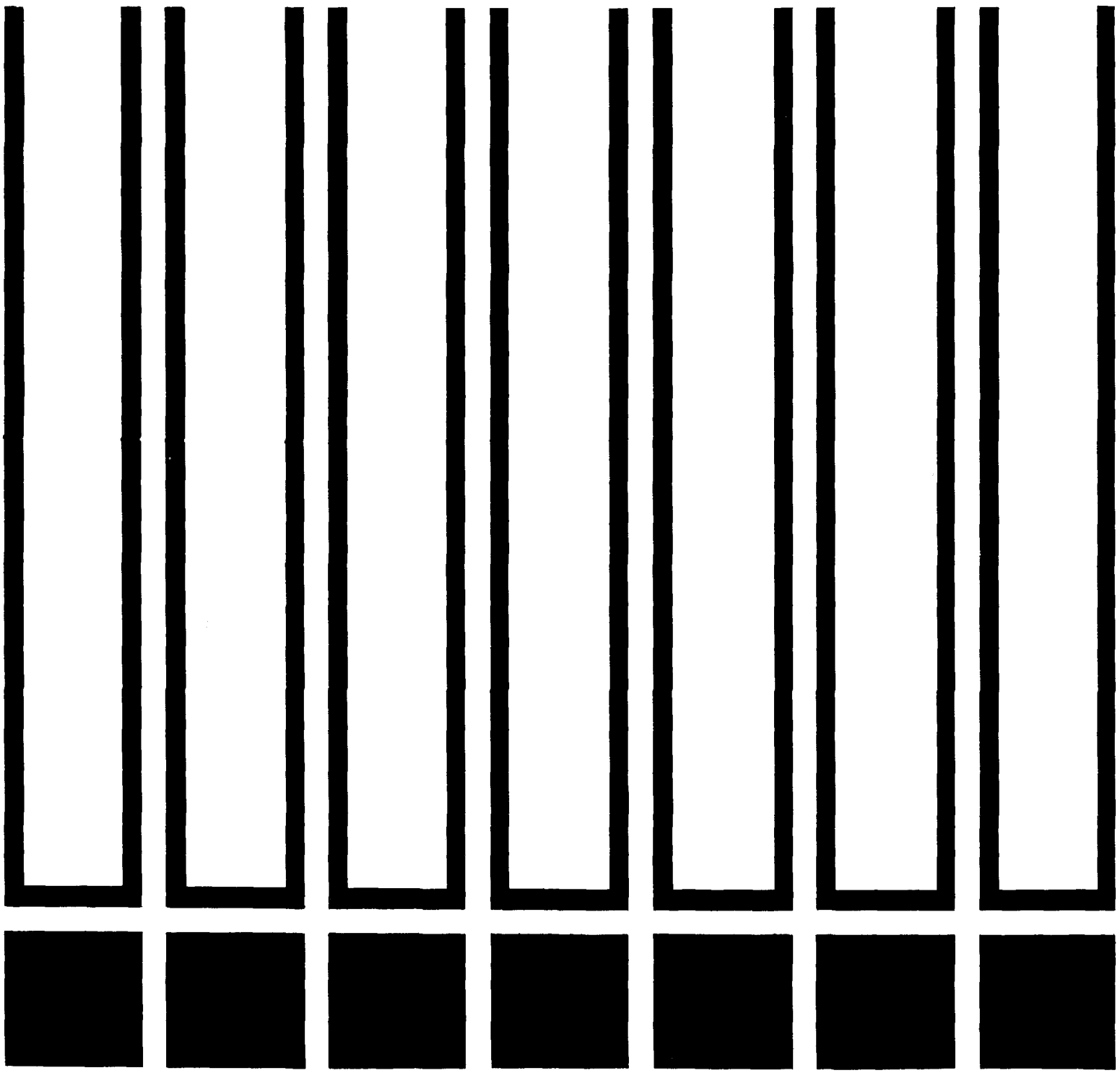

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service / Center for Disease Control

National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO CADMIUM

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

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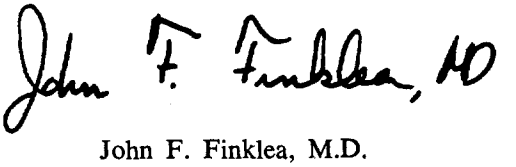
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on cadmium by members of my staff, by the Review Consultants on Cadmium, by the ad hoc committees of the American Industrial Hygiene Association and of the Society of Toxicology, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Edwin C. Hyatt on work practices and respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on cadmium. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.



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Director, National Institute for
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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for cadmium. The Division review staff consisted of J. Henry Wills, Ph.D. (Chairman) and Frank L. Mitchell, D.O., with Philip J. Bierbaum (Division of Surveillance, Hazard Evaluations, and Field Studies) and Robert L. Roudabush, Ph.D.

The University of Cincinnati, College of Medicine, developed the basic information for consideration by NIOSH staff and consultants under contract No. HSM-99-72-87. Keith H. Jacobson, Ph.D., had NIOSH program responsibility and served as criteria manager.

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Contents

I. RECOMMENDATIONS FOR A CADMIUM STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to cadmium in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of workers for up to a 10-hour workday, 40-hour week, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of exposure to cadmium on the health and safety of workers. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. The criteria and the standard will be subject to review and revision as necessary.

"Cadmium" refers to elemental cadmium and all cadmium compounds. An "action level" is defined as half the time-weighted average concentration environmental limit of cadmium. "Occupational exposure to cadmium" is defined as exposure to cadmium at a concentration greater than the action level. Exposures at lower environmental concentrations will not require adherence to the following sections, except for Section 6(b) and 7(d).

Section 1—Environmental (Workplace Air)

(a) Concentration

Occupational exposure to cadmium shall be controlled so that workers are not exposed to cadmium at a concentration greater than 40 micrograms per cubic meter of air (40 μg Cd/cu m) determined as a time-weighted average (TWA) exposure concentration for up to a 10-hour workday, 40-hour workweek, or at a ceiling concentration greater than 200 μg Cd/cu m for any 15-minute sampling period.

(b) Sampling and analysis

Sampling in the work environment shall be performed by the method provided in Appendix I or by a method with at least equivalent efficiency. Samples shall be analyzed by the method provided in Appendix II or by a method shown to be at least equivalent in precision and sensitivity.

Section 2—Medical

Medical monitoring shall be made available to all workers subject to occupational exposure to cadmium.

(a) Preplacement examinations shall be made available to new or reassigned employees prior to job placement, and, within 6 months of the promulgation of a standard based on these recommendations, to employees already engaged in work involving exposure to cadmium.

Preplacement examinations shall include comprehensive work and medical histories, a 14" X 17" P.A. chest X-ray, measurement of forced vital capacity (FVC) and forced expiratory volume during the first second (FEV_1), measurement of blood pressure, blood analysis (blood urea nitrogen, complete blood count, and serum glutamic oxaloacetate transaminase or other liver enzymes), and urinalysis (microscopic examination, sugar determination, quantitative protein determination, and specific gravity measurement). A judgment of the worker's ability to work in positive or negative pressure respirators shall be made.

The method for protein determination in urine shall be quantitative and capable of detecting low molecular weight proteins (see Appendix III). Determination of urine cadmium levels is also recommended.

(b) Periodic examinations shall also be made available. Except for urine protein determinations, which shall be made available every 4 months, these examinations shall be offered yearly, or as otherwise directed by the responsible physician.

These periodic examinations shall include interim work and medical histories, urinalysis (with quantitative protein determinations every 4 months), pulmonary function tests (FVC and

FEV_1), and blood pressure. Chest radiographs shall be taken if judged necessary by the responsible physician.

In addition, blood analysis, palpation of the prostate in male workers over 40 years old, and monitoring of urine cadmium concentrations are also recommended. If the concentration of cadmium in the urine rises above 10 μg/liter, an investigation of the cause, such as environmental exposures, personal and industrial hygiene practices, and nonoccupational exposure, should be conducted.

Reassessment of occupational exposure, work practices, and personal habits shall be undertaken if FVC or FEV_1 becomes reduced 15% or more or the ratio FEV_1/FVC is reduced 10% or more than would be expected from the age and smoking habits of the person examined, if persistent symptoms of respiratory tract disease develop, if there are frequent upper or lower respiratory infections, or if persistent proteinuria or other abnormal laboratory or clinical findings relatable to cadmium toxicity develop.

Smokers should be counseled on their possibly increased risk of chronic respiratory disease.

(c) At termination of or transfer from employment involving occupational exposure to cadmium, a comprehensive examination including the components of (a) above shall be offered.

(d) Pertinent medical records shall be retained for 20 years after the last occupational exposure to cadmium. These records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

Section 3—Labeling and Posting

(a) Containers

Shipping and storage containers or packages containing cadmium or cadmium compounds shall bear the following label:

DANGER!

CONTAINS * POISONOUS FUMES MAY BE FORMED ON HEATING HARMFUL IF INHALED OR SWALLOWED AVOID CONTACT WITH SKIN, EYES, AND CLOTHING WASH HANDS THOROUGHLY AFTER HANDLING

Avoid breathing fume, dust, or mist Keep container closed Use only with adequate ventilation

*Complete by inserting "cadmium" or name of cadmium compound.

(b) Work areas

Locations or areas where cadmium dust or fume are likely to be generated shall be designated with clearly visible warning signs as shown below:

DANGER!

CADMIUM (Cd)

Cadmium Fume (or Dust) Areas Authorized Personnel Only Breathing Fume (or Dust) May Cause Immediate or Delayed Injury

No Smoking

Respirators Are Located.....**

**Give location of respirators.

This sign shall be printed in English and in the predominant language of non-English-speaking workers. All employees shall be trained and informed of the hazards and the hazardous areas. All illiterate workers shall receive special attention.

Section 4—Personal Protective Equipment and Clothing

Engineering controls shall be used if needed to maintain airborne cadmium concentrations at or below the limits recommended in Section 1. Compliance with these workplace environmental limits by the use of respirators is permitted only during installation and testing of engineering controls, during performance of nonroutine maintenance or repair, during single operations, or during emergencies. When use of a respirator is permitted, it shall be selected and used in accordance with the following requirements:

(a) For the purpose of determining the type of respirator to be used, the employer shall measure the concentrations of cadmium in the workplace initially and thereafter whenever control, process, operation, worksite, or climate changes occur that are likely to increase the concentration of airborne cadmium.

(b) The employer shall ensure that no worker is exposed to cadmium in excess of the recommended limits because of improper respirator selection, fit, use, or maintenance.

(c) A respiratory protection program meeting the requirements of 29 CFR 1910.134, which incorporates the American National Standard Practices for Respiratory Protection, Z88.2-1969, shall be established and enforced by the employer.

(d) The employer shall provide respirators in accordance with Table I-1, and shall ensure that employees use the respirators provided in a proper manner when wearing of respirators is required.

(e) Respirators selected from those described in Table I-1 shall be those approved under the provisions of 30 CFR 11.

(f) The employer shall ensure that employees are properly instructed in the use of respirators assigned to their use and on how to test for leakage, proper fit, and proper operation.

(g) Respirators specified in Table I-1 for use in atmospheres of higher concentrations of airborne cadmium may be used in atmospheres of lower cadmium concentrations.

(h) The employer shall establish and conduct a program of cleaning, sanitizing, inspecting, maintaining, repairing, and storing of respirators, to ensure that employees are provided with clean respirators that are in good operating condition.

(i) The employer shall periodically monitor the use of respirators to ensure that the proper type of respirator is worn, to evaluate the effectiveness of the respiratory protection program, and to eliminate any deficiencies in use and care of respirators.

Section 5—Informing Employees of Hazards from Cadmium

(a) Workers initially assigned or reassigned to jobs involving occupational exposure to cadmium shall be informed of the hazards, symptoms of overexposure (including information on the characteristics of onset and stages of illness), appropriate procedures to be taken in the event of an emergency, and precautions to ensure safe use and to minimize exposure. They shall be advised of the availability of relevant information, including that prescribed in (c) below. This information shall be accessible to each worker occupationally exposed to cadmium.

(b) A continuing education program, conducted by a person or persons qualified by experience or special training, shall be instituted to ensure that all workers have current knowledge of job hazards, proper maintenance procedures and cleanup methods, and that they know how to use respirators correctly. It shall include a description of the general nature of the medical surveillance procedures and why it is advantageous to the worker to undergo these examinations.

(c) Required information shall be recorded on a "Material Safety Data Sheet" as specified in Appendix IV or on any other form approved for the purpose by the Occupational Safety and Health Administration, US Department of Labor.

Section 6—Work Practices

(a) Exhaust Systems

Operations creating workplace exposure to cadmium shall be enclosed to the maximum extent practicable and be provided with local exhaust ventilation unless appropriate air sampling and analysis have demonstrated that concentrations are at or below the environmental limits. Methods other than enclosure and ventilation for meeting exposure limits to cadmium may be used if they bring concentrations in workplace air to or below the environmental limits. Effluent air shall be cleaned to meet any emission standards that may become promulgated. Air from the exhaust ventilation system shall not be recirculated into the workplace.

Enclosures, exhaust hoods, and ductwork shall be kept in good repair so that design airflows are maintained. Airflow shall be measured at each hood at least semiannually, and preferably monthly. Continuous airflow indicators are recommended, such as water or oil manometers properly mounted at the juncture of fume hood and duct throat (marked to indicate acceptable airflow). A log showing design airflow and results of semiannual inspections shall be kept.

(b) Welding, Brazing, and Thermal Cutting

Welding, brazing, or thermal cutting of material containing cadmium shall be performed using local exhaust ventilation demonstrated by air sampling and analysis to keep cadmium concentrations within the limits of Section 1. For single operations where local exhaust ventilation is not available, where air sampling has not been performed,

TABLE I-1

RESPIRATOR SELECTION GUIDE

Cadmium Concentration	Respirator Type
Less than or equal to 0.4 mg/cu m	(1) Half-mask respirator with high-efficiency filter(s). (2) Type C demand-type (negative pressure) supplied-air respirator with half-mask facepiece.
Less than or equal to 2.0 mg/cu m	(1) Full facepiece respirator with high-efficiency filter(s). (2) Type C demand-type (negative pressure) supplied-air respirator with full facepiece. (3) Self-contained breathing apparatus with full facepiece in demand mode (negative pressure).
Less than or equal to 40 mg/cu m	(1) Powered air-purifying (positive pressure) respirator with high efficiency filter(s). (2) Type C continuous-flow (positive pressure) supplied-air respirator.
40 mg/cu m or greater or unknown	(1) Combination supplied-air respirator, pressure-demand type, with auxiliary self-contained air supply. (2) Self-contained breathing apparatus with full facepiece in positive pressure mode.

or where air sampling has demonstrated a likelihood of overexposure to cadmium fume or dust, respirators shall be provided and worn as specified in Section 4.

Where molten cadmium is used or formed, temperatures should be kept as low as possible consistent with the requirements of the operation to prevent excessive fume generation. Additions of cadmium should be made in the manner generating the least fume. Wherever possible, this should be accomplished by automatic controls, with recording of temperature and use of alarms or indicators for higher temperatures.

(c) Emergency Procedures

Emergency procedures shall be established for any event which may result in substantial release of airborne cadmium. Such procedures shall include provision for appropriate respirators as specified in Section 4.

Specific emergency procedures shall be designed for fires, to protect both in-plant workers and firefighters.

(d) Work Clothing

Workers shall wear work clothing consisting of at least hat, shirt or blouse, pants or skirt, and shoes. Work clothing and street clothing shall be exchanged at the beginning and the end of each workday, so that work clothing will not be worn outside the workplace. The employer shall provide for proper laundry of clothing and shall instruct launderers on procedures to be taken to avoid inhalation of cadmium-containing dusts.

Section 7—Sanitation Practices

(a) Where there is cadmium-containing dust, cleaning should be performed by vacuum pickup or wet mopping. No dry sweeping or blowing shall be permitted.

(b) Emphasis shall be placed upon prompt cleanup of spills, repair of equipment and leaks, proper storage of materials, and collection of cadmium-containing dust.

(c) Cadmium-containing and cadmium-plated metal parts should be kept separate from parts not containing cadmium and marked appropriately so that accidental exposures resulting from welding and cutting will not occur.

(d) Facilities shall be maintained to protect foodstuffs and food consumption areas from contamination by materials containing cadmium. Food storage, handling, and consumption shall be separate from cadmium work areas. Smoking or carrying uncovered tobacco or tobacco products in cadmium work areas shall be prohibited.

(e) Adequate handwashing and shower facilities shall be provided. Workers shall wash their hands before eating or before using tobacco to prevent their absorbing additional amounts of cadmium compounds.

Section 8—Monitoring and Recordkeeping

Workers are not considered to be occupationally exposed to cadmium if environmental concentrations, as determined on the basis of an industrial hygiene survey to be performed within 90 days of the promulgation of a standard, do not exceed the action level, ie, half the recommended TWA environmental limit, or if there is no operation, storage, or handling of cadmium in any form or

contamination of workplace air by cadmium from other sources. These industrial hygiene surveys shall be repeated at least every 3 years and within 30 days after any process or operating change likely to result in increases of airborne concentrations of cadmium. Records of these surveys, including the basis for concluding that airborne concentrations of cadmium are at or below the action level, shall be maintained until the next survey has been completed.

The following requirements apply to occupational exposure to cadmium, ie, to workplaces where the action level is exceeded.

(a) Personal monitoring

A program of breathing zone or personal monitoring shall be instituted to identify and measure the exposure of all employees occupationally exposed to cadmium. This sampling and analysis shall be conducted every 3 months on at least 25% of the workers so that each worker's exposure is measured at least every year; this frequency and fraction of employees sampled may be different if so directed by a professional industrial hygienist. Sufficient numbers of samples shall be collected and analyzed to permit construction of valid estimates of the TWA and ceiling concentration exposures of workers during each workshift; the number of TWA and ceiling concentration determinations for an operation shall be based on such factors as mobility and job functions of workers in that operation. If monitoring of any worker shows exposure in excess of either recommended environmental limit, additional monitoring shall be promptly initiated. If confirmed, control procedures shall be instituted as soon as possible; these may precede and obviate confirmatory monitoring if the employer desires. Affected employees shall be advised that exposures have been excessive and be notified of the control procedures being implemented. Monitoring of these employees' exposures shall be conducted at least as often as every 30 days and shall continue until 2 successive samplings at least a week apart confirm that exposure no longer exceeds recommended limits. Normal monitoring may then be resumed.

(b) Recordkeeping

Environmental monitoring records shall be maintained for at least 20 years. These records shall include methods of sampling and analysis used, types of respiratory protection used, and TWA and ceiling concentrations found. Each employee shall be able to obtain information on his own environmental exposures. Environmental records shall be made available to designated representatives of the Secretary of Labor and of the Secretary of Health, Education, and Welfare.

Pertinent medical records shall be retained for 20 years after the last occupational exposure to cadmium. Records of environmental exposures applicable to an employee should be included in that employee's medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing impairment of health from occupational exposure to cadmium. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "... develop criteria dealing with toxic materials and harmful physical agents and substances which will describe... exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health and safety of workers from exposure to hazardous chemical and physical agents. The criteria and recommended standard should enable management and labor to develop better engineering controls and more healthful work practices and should not be used as a final goal.

These criteria for a standard for cadmium are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of cadmium as applicable under the Occupational Safety and Health Act of 1970.

The standard was not designed for the population-at-large, and any extrapolation beyond general occupational exposures is not warranted. It is intended to (1) protect against injury from cadmium, (2) be measurable by techniques that are valid, reproducible, and available to industry and official agencies, and (3) be attainable with existing technology.

The criteria document reviews sources, uses, distribution, and biologic effects of, and sampling and analytical methods for, cadmium. In selecting from extensive scientific and technical literature on cadmium to prepare this review, emphasis has been given to those studies most relevant to occupational exposure and, where many investigations give similar information, to the more basic or recent articles. For additional information, various reviews are suggested. These include *Cadmium in the Environment* (second edition) by Friberg and coauthors[1] and a supplement *Cadmium in the Environment III*,[2] a shorter review by Riihimaki,[3] the WHO-IARC review of cadmium,[4] EPA's *Scientific and Technical Assessment Report on Cadmium*, [5] a study of *Environmental Impact of Cadmium* by Fleischer et al,[6] *Cadmium, The Dissipated Element*, by Fulkerson and Goeller,[7] and a book *Cadmium* on technology and properties of cadmium and its compounds by Chizhikov from the USSR, available in an English translation.[8]

Cadmium is one of the more thoroughly investigated workplace hazards, and considerable information about occupational health problems associated with cadmium has been developed. Nevertheless, there are important gaps in the knowledge of toxic effects in man at concentrations of cadmium encountered in the workplace. Important gaps include possible effects on male and female gonads, possible birth defects in offspring of workers, and the possibility of cancer, especially among male workers. Conclusions on these and other points arrived at in this document should be verified, refuted, or modified by additional research. In addition, better data are needed on absorption, distribution within the body, accumulation, especially in the kidney, and excretion of cadmium. Research in this area may resolve several questions, including questions about the significance of cadmium in blood and urine to health status and to cadmium absorption.

2

III. BIOLOGIC EFFECTS OF EXPOSURE

Metallic or elemental cadmium (Cd), which has atomic number 48 and atomic weight 112.40, has a silver-blue-white appearance. The use of cadmium as a protective coating relies on the resistance of the oxide to further oxidation.[8 (p 8)]

A brown aerosol of cadmium oxide is formed on ignition of cadmium vapor.[9] The metal has a boiling point of 765 C, or 1409 F,[10] and the vapor is readily formed under conditions which allow other metals to be worked. Cadmium will also melt at a low temperature of 321 C, or 610 F,[10] so sufficiently heated cadmium can flow to an area where volatilization can occur. Physical properties of cadmium are summarized in Table XIV-1.

The electrical conductivity of cadmium is less than that of silver or copper, but greater than that of iron. The addition of cadmium to copper, for example, reduces the conductance and the breakage and wear; this yields wire and electrical contacts of improved functional properties. Cadmium is also used in other alloys to produce a material which is more readily machined or melts at a lower temperature.[8 (pp 66-67)]

The principal cadmium ore is greenockite, cadmium sulfide,[9] but it is not a major source of metal production. Cadmium occurs in economically recoverable form only with the sulfide ores of other elements, particularly zinc.[9] Cadmium is obtained commercially as a byproduct in the refining of zinc, lead-zinc, and copper-lead-zinc ores and these are the primary sources of cadmium. Metallic cadmium was formerly prepared by fractional distillation, but this has increasingly been replaced by electrolytic methods.[9]

Estimated US consumption of cadmium (production plus imports) ranged from 4.2 to 6.9 million kilograms in the 1961-1970 period, with the highest consumption in 1969 and the lowest in 1970.[11] The average estimated annual consumption for the period 1961-1970 was 5.3 million kilograms and for the previous decade, 4.4 million kilograms. World production in 1970 was reported to be 35 million pounds, or almost 16 million kilograms.[4]

Electroplating is and has been the leading use for cadmium, consuming from 45 to 60% of the amount produced each year. About one million kilograms/year are used for stabilizers in plastics, and somewhat less than a million kilograms in pigments, with plastics a large consumer of the pigments.[12] One-quarter to one-half million kilograms of cadmium are used annually as an alloying agent in low melting-point brazing alloys, in copper for automobile radiators, in silver-cadmium electrical contacts, and in other metallurgical alloys. These 4 major categories account for 80-90% of the cadmium used, with the rest distributed among minor uses such as nickel-cadmium batteries, fungicides, photography, and television picture tubes.

Cadmium dusts, fumes, and mists are commonly present in some smelting processes involving zinc, copper, and lead as well as in specific processes for extracting cadmium.[13]

NIOSH estimates that 100,000 persons in the work force are potentially exposed to cadmium.

Extent of Exposure

Both the natural occurrence of cadmium and zinc in soil and the application of superphosphate fertilizers[14] result in detectable concentrations of cadmium in vegetables, land animals, and fresh water fish.[15-19] The cadmium content of sea water results in measurable cadmium concentrations in seafood. Cadmium has been reported to accumulate in certain animal tissues and to undergo biologic concentration in oysters.[20]

(a) Community Air

The National Air Sampling Network reported in 1966 and 1967 that 73% of the samples in 136 cities contained less than the minimum detectable concentration of 10 ng/cu m.[21] One study of particle size distribution gave a mass median

aerodynamic diameter (mmad) of 3.1 μm in Cincinnati, Ohio, and an estimated 10 μm in Fairfax, Ohio.[22] These limited data should probably be used with some caution.

(b) Water

Both surface waters[23] and drinking water[24] have been analyzed for cadmium. Analyses of 194 finished water supplies serving 139 municipalities showed a mean cadmium concentration of 0.008 ppm[24]; in 16% of the analyses, the Public Health Service drinking water standard of 0.01 ppm was exceeded. A more recent (1970) review[25] of 969 water systems indicated that 0.2% had concentrations in excess of the PHS drinking water standard of 10 μg/liter. Cadmium concentrations in drinking water can be increased when the water flows through either galvanized or polyvinyl chloride pipe.[15] Water containers soldered with silver-cadmium alloy may also pose a risk of contamination.

(c) Food

Dietary intake of cadmium has been reported by several investigators.[16-19,26-31] Duggan and Corneliussen[31] estimated a daily intake in 1969-70 of 2 μg Cd from dairy products, 3 from meat, fish, and poultry products, 10 from grains and cereals, 8 from potatoes, 3 from leafy vegetables, less than 1 from legumes, 1 from root vegetables, 2 from fruits, 1 from fats and shortening, 1 from sugar and adjuncts, and 5 from beverages. These estimates have not been adjusted for mass or caloric intake and are probably high for the average adult diet.

The UN Food and Agriculture Organization and World Health Organization[32] have estimated from limited results of total diet studies that dietary intake of cadmium varies according to country from 50 or less to 150 μg/day. On the assumption that renal damage may occur when cadmium concentrations in the renal cortex exceed 200 mg/kg wet weight, FAO/WHO proposed a provisional tolerable weekly intake of cadmium of 400-500 μg for each individual.

Another source of cadmium exposure is from tobacco products. Side-stream cigarette smoke was found to contain 0.4-0.7 μg cadmium/cigarette, while the mainstream cigarette smoke contained up to 0.1 μg cadmium/cigarette.[33]

Historical Reports

Bonnell[34] has commented that the occupational toxicity of cadmium was noted as early as 1858 by Sovet,[35] who reported a case of vomiting, cramps, and severe abdominal pain due largely, probably, to ingestion of cadmium carbonate used as a silver polish. Inhalation of the dust and swallowing of the material impacted on the mucosa of the upper respiratory tract may have contributed to the intoxication, which had the characteristics of acute poisoning by oral ingestion of cadmium rather than from inhalation of a cadmium-containing material. According to Christensen and Olson,[36] there were only 64 exposures reported in the literature up to 1945, about 15% of them fatal. However, Fairhall's[37] compilation of cadmium poisoning by ingestion cited 20 cases prior to 1940 and 689 in the period 1941-1946.

Bonnell[34] cited Stephens, in 1920, and Mancioli, in 1940, who described cases of chronic illness due to occupational exposure to cadmium. During World War II, the superimposition of nutritional deficiencies onto cadmium exposure was suggested by Nicaud and coworkers[38] as contributing to bone disease (osteomalacia) in cadmium workers in France. Cadmium is also believed to have been one causal factor in the development of Itai-Itai ("ouch-ouch") episodes in Japan.[1 (pp 137-161),39-41]

Effects on Humans

This section reviews the effects of cadmium on humans, mostly from evidence developed in epidemiologic studies, in terms of types of effects such as organs or organ systems affected. Many of these studies together with additional ones are reviewed, often in more detail, in the section on *Epidemiologic Studies*. In the latter section, there is more emphasis on population studies and on a correlation of human effects with airborne cadmium concentrations.

(a) Pulmonary Effects

(1) Acute Effects

Acute intoxication from exposure to cadmium oxide fumes in concentrations of at least several milligrams/cubic meter has a characteristic clinical picture.[42-45] Initially, there are virtually no symptoms; these usually appear 4-10 hours later, when dyspnea, cough, and not infrequently a feeling of constriction in the chest develop. On occasion, workers may complain of substernal chest pain or

a burning sensation in the chest that is accentuated by coughing. Some may also develop a flu-like syndrome characterized by shaky chills and myalgia localized in the back and limbs. Under this latter circumstance, the illness may be mistaken for metal-fume fever. In any event, acute pulmonary edema may develop within 24 hours. In such cases, physical examination reveals an acutely ill patient with rales heard on auscultation of the chest. Chest X-rays show bilateral pulmonary infiltrates suggestive of pulmonary edema. Pulmonary function testing, when performed, has shown a decreased forced vital capacity (FVC) and forced expiratory volume during the first second (FEV_1). In addition, there is evidence of abnormal gas exchange with a markedly reduced carbon monoxide diffusion capacity. The subsequent clinical course is unpredictable. In most cases, the symptoms resolve over the next week; but in approximately 20% of the people exposed, the dyspnea is progressive and may be associated with wheezing or hemoptysis. In cases that are progressive, death characteristically occurs within the first week after exposure. Chronic sequelae include pulmonary fibrosis and "honeycomb" lung. There are interstitial fibrosis, hypertrophy of circular muscle of the media and formation of longitudinal muscle in the intima of muscular pulmonary arteries, hypertrophy of the media of bronchial arteries, atheromas of the intima of elastic pulmonary arteries, thickening of the elastic lamina and pronounced proliferation of the fibroelastic component of the intima of pulmonary veins, and, occasionally, evidence of recanalized thrombi in both arteries or veins.[42,46] In addition, there has been evidence in two acutely intoxicated men of liver changes.[47,48]

The stages of acute pulmonary edema and acute interstitial pneumonia have been further studied by autopsy on humans exposed to cadmium by inhalation.[42,44,49,50] Townshend[43] in 1968 reported one case of pulmonary edema caused by acute cadmium poisoning which he followed over a period of 4 years. Serial pulmonary function tests showed improvement in lung function during the first 6 months. Four years later, carbon monoxide diffusion capacity was normal, but the forced vital capacity was less than 80% of the predicted value.

There are few data related to the acute dose-response relationship for cadmium in humans. However, estimates of lethal concentrations of 2,500,[51] 2,600,[44] and 2,900[52] mg-min/cu m have been made. These calculations have been based on some estimations or assumptions about the airborne concentrations of cadmium after fatal exposures to cadmium oxide, the pulmonary ventilation, the percentage of cadmium retained, and the concentrations of cadmium within the alveoli of the lungs. While some uncertainties exist, it seems reasonable to conclude that a probably lethal exposure to CdO fume consists of breathing about 5 mg/cu m during an 8-hour period (this is equivalent to 2,400 mg-min/cu m.) This concentration probably should not be considered to be the lowest which can give rise to fatal poisoning, however. A likely interpretation of data obtained through animal experimentation[49] indicates that a concentration of cadmium oxide fumes of about 1 mg/cu m inhaled during an 8-hour period may be dangerous for humans. Sufficient data are not available for making similar estimations for other forms of cadmium.

Blejer et al[47,48] described two cases of cadmium oxide fume poisoning in a silver brazing operation. The first man, exposed at a concentration thought to be above 1 mg Cd/cu m, became acutely ill and died about 3 days later. Post-mortem examination showed he had pulmonary edema, bronchial deepithelialization, extreme hemorrhagic congestion of the lungs, and a "nutmeg" liver. The brazing operation was moved outdoors, whereupon a second worker became ill. He was hospitalized, was administered oxygen under positive pressure, and recovered. Laboratory examinations showed elevated serum glutamic oxaloacetic transaminase (SGOT) and serum bilirubin, suggestive of hepatic damage. Reconstruction of the circumstances of the exposure led to several estimates of the breathing zone concentrations, viz, 10, 20, and 140 μg Cd/cu m. The worker was estimated to have been exposed for about 9⅔ hours, apparently over a period of 3 days.[48] The authors[47] suggested that simultaneous exposure to fumes of cadmium, copper, and zinc (probably as the oxides) and to fluoride gases such as hydrogen fluoride and carbonyl fluoride contributed to the intoxication in both cases.

(2) Chronic Effects

Chronic cadmium inhalation has been reported to cause pulmonary emphysema in man.[53-56] Friberg[57] investigated male workers exposed to cadmium oxide dust in an alkaline storage-battery

factory in Sweden. He found that shortness of breath was a common complaint, and pulmonary function studies revealed increased residual volume in relation to total lung capacity in workers exposed for an average of 20 years. Results from exercise studies were abnormal in many of these individuals. Baader[58] studied a worker who had become ill after being exposed to cadmium oxide dust in a battery factory. From clinical and X-ray evidence, he had "considerable emphysema." He died at the age of 39, apparently from right heart failure. Post-mortem examination showed bullous emphysema, fibroplastic peribronchitis and primary peribronchial interstitial pneumonia of all lobes of the lungs, and purulent bronchitis. From evidence of lesions of various ganglia, Baader suggested nerve tissue lesions as a contributing factor in pathogenesis of the obstructive lung disease. Lane and Campbell[53] described the development of emphysema within 2 years after the first exposure to cadmium. Kazantzis and associates[54] found no evidence of pulmonary abnormalities in workers exposed to cadmium sulfide dust 12-14 years. However, 4 of 6 of those employed for over 25 years had respiratory impairment, including 1 who died of emphysema. Holden[59] found on pulmonary function testing that 8 of 23 men exposed to cadmium 12-39 years had abnormalities suggestive of emphysema. This emphysema may be due to cadmium's inhibition of antitrypsin. Chowdhury and Louria[60] added 5-50 μg/ml Cd(II) to human plasma and found an inhibition of α_1-antitrypsin with a decrease in trypsin inhibitory capacity. Other metals tested, viz, Pb(II), Hg(II), Fe(II), Zn(II), and Ni(II), had little or no effect in concentrations equimolar with that of Cd(II).

Investigations utilizing pulmonary function testing[55] in both cadmium-exposed and control groups have suggested a higher incidence of obstructive lung disease among the exposed workers. There have been several other studies[61-64] in which no pulmonary effects from chronic cadmium intoxication were observed. At least some of these involved exposures at lower concentrations or for shorter exposure times.

(b) Renal Effects

The most common abnormality found in workers exposed to cadmium is proteinuria.[54,55,65] Friberg[55] found proteinuria in 81% of 43 workers exposed to cadmium for an average of 20 years in the alkaline storage battery industry and pointed out that the protein excreted was not the protein conventionally excreted after kidney injury, ie, it was of low molecular weight, about 20,000-30,000. Piscator[66] examined protein in urines of 79 cadmium workers, 55 of whom had been previously studied by Friberg.[55] He found an average excretion of protein of 50 mg/day in 10 healthy, unexposed subjects and 70-2,600 mg/day in cadmium workers. In men excreting more than 150 mg/day, the electrophoretic pattern of urine protein was characterized by a low albumin content and increased contents of α_2-, β-, and γ-globulins. In 75% of the men excreting more than 400 mg/day, there was a distinct β-globulin peak. In a few, he found a post-γ-globulin fraction. Cadmium workers also had a significantly higher concentration of γ-globulin and of protein-bound hexoses in serum than did unexposed workers. Potts[65] studied 70 battery workers and found proteinuria in 34% of those exposed 10-19 years, and 82% of workers exposed for over 30 years. Kazantzis and associates[54] noted that duration of exposure to cadmium was important in the development of proteinuria. They found no proteinuria in those exposed for less than 2 years; proteinuria was found in 3 of the 4 exposed for 12 to 14 years and in all of those exposed for 25 years or more. The proteinuria was characterized by excretion of urinary protein of low molecular weight, between 20,000 and 25,000. The pathogenesis of the proteinuria has not been fully delineated, but Vigliani[67] has suggested that protein may appear in the urine because tubular-bound cadmium interferes with the ability of the normal kidney to catabolize immunoglobulins and other proteins. Others[1 (pp 105-106), 68,69] believe that it results from a decreased reabsorption of normally present protein by the renal tubules. This latter view seems more likely, ie, it is likely that low molecular weight proteins appearing in the urine of persons intoxicated by cadmium would have been reabsorbed by the normal kidney, so that their appearance in urine is an early sign of renal dysfunction. However, as Friberg and associates[1 (p 112)] have suggested, both altered catabolism and altered reabsorption of proteins may exist.

There are few data on acute renal effects. Bilateral renal cortical necrosis has been reported in a fatal case.[44] The concentration of cadmium in the kidney was given as 5.7 ppm wet weight,

which seems not abnormally high in view of the report[70] that the concentrations of cadmium in renal cortices of people 50 years old from several different countries range from 15 to 50 μg/g; even higher concentrations of 60-125 μg/g have been found in kidneys from areas of Japan regarded as not polluted with cadmium.

Other reported evidence of disturbed renal tubular function besides proteinuria includes the finding of glucosuria,[54,61,71-74] amino aciduria,[54,71,75] decreased urine-concentrating ability,[55,71] and abnormalities in renal handling of uric acid, calcium, and phosphorus.[54,71] However, proteinuria can appear alone without the other above-mentioned changes, so that it may often be the earliest sign of renal dysfunction in cadmium intoxication.

A few instances of reduced glomerular filtration rates in cadmium workers have been reported.[55,71,76]

Renal stone formation has been reported in cadmium workers in Sweden.[55,76] Ahlmark and coworkers[76] found that 44% of a group of workers exposed to cadmium dust for more than 15 years had a history of renal stones. When examined, the stones were found to be composed mainly of calcium phosphate.[77] Other investigators have noted a high prevalence of renal stones in nonproteinuric workers.[71,77] Some workers had hypercalcinuria without proteinuria. The high incidence of kidney stones may be the result of disturbed excretion of calcium and phosphorus, as suggested by Axelsson.[77] Information from autopsy and biopsy material of kidneys is limited. Friberg et al[1] (pp 107-108) reviewed findings of several of their published studies and of unpublished studies of autopsy and biopsy material and concluded that the morphologic changes are confined mainly to the proximal tubules, with less evidence of effect in the glomeruli. Kidney cadmium levels were measured and, in general, tended to be lower when morphologic changes were present than when such changes were absent or minor. On this basis, it seems that renal damage following cadmium exposure may result in a decrease in the concentration of cadmium within the kidney. If this is so, a worker with significant renal damage may have a lower concentration of cadmium within his kidneys than one with only slight renal disturbance.[1] (p 107) There is support for this inference from experimental studies in animals, reviewed later.

(c) Olfactory Effects

A potential consequence of cadmium exposure is damage to the olfactory apparatus, which may result in total anosmia. As with lung and kidney damage, duration and concentration of exposure are probably important factors. Potts[65] found olfactory damage in 53-65% of workers exposed 10-29 years and in 91% of those exposed for more than 30 years. Thirty-seven percent of the 43 workers studied by Friberg[55] showed olfactory impairment. Adams and Crabtree[78] reported cases of hyposmia and anosmia among workers exposed to cadmium oxide dust as well as to nickel dust, in an alkaline-battery operation. A group of 106 battery workers were compared with 84 age-matched controls. Olfactory acuity was judged from each subject's evaluation of his own acuity and from a phenol smelling test. Battery workers reported significantly more anosmia (15% vs 0%) and did less well on the phenol smelling test (27% vs 5%). There was a positive correlation between proteinuria and anosmia; 17 workers with proteinuria also were anosmic. Examination of noses showed many cases of local irritation from dust, some submucosal fibrosis in mild cases of deficient olfactory acuity, and cases of ulceration, occasionally with dry crusting, in more advanced cases. Biopsy material from one case showed a mild nonspecific submucosal chronic inflammation with a few small loose focal accumulations of lymphocytes and a few widely scattered eosinophils. The authors attributed the anosmia to exposure to either cadmium or nickel, or to a mixture of the two. The population studied by Friberg[55] was also exposed to nickel. Potts[65] did not report nickel exposures, but the workers made batteries, so there were undoubtedly exposures to nickel dust, as well as to cadmium. However, Tsuji et al[79] reported that several workers exposed to cadmium in a zinc refinery, without evidence of exposure to nickel, had a so-called insensitiveness to smells.

(d) Hematopoietic System

Acute effects on the blood after respiratory exposure at a high concentration of cadmium have been noted both in humans and in animals.[44,80] Elevated hemoglobin in some human subjects may well have been the result of hemoconcentration from pulmonary edema.[44]

Anemia has been described in workers exposed for a long time to cadmium oxide dust and fume.[38,55,81] The anemia was usually moderate. In a group of workers exposed to cadmium 5-30 years,

Piscator, in unpublished studies reviewed by Friberg, Piscator, Nordberg, and Kjellstrom[1] (p 114) reportedly found a significant correlation between high cadmium and low hemoglobin concentrations in blood. Bone marrow examinations of 19 cadmium-exposed workers revealed no pathologic changes.[55] Peripheral eosinophilia has been reported to occur in some workers.[38,55,62]

(e) Cardiovascular Effects

There are some controversial data on a possible role of cadmium in hypertension. Epidemiologic investigations of the general population have noted a positive correlation between cardiovascular disease and ambient cadmium levels[82]; no distinction was made in these studies between hypertensive and arteriosclerotic diseases. Perry and Schroeder[83] reported that hypertensive patients had increased urinary cadmium and, to a lesser extent, increased urinary manganese levels, as compared with normotensive individuals. In 187 adults studied at autopsy, the 17 suffering from hypertension had either higher concentrations of cadmium or higher cadmium-to-zinc ratios in their kidneys than the normotensive ones.[84] A correlation between cadmium level and mortality from cardiovascular disease in the United States has been reported[82] but cannot be considered to be indicative of a direct cause-effect relationship because the amount of cadmium absorbed from inhaled air during a day in the city of the US with the highest airborne cadmium concentration (Chicago) would be no more than 12% of the total intake. It could be as little as 1% of the total intake, depending on the composition of the diet. Schroeder[85] has commented on the association between hypertensive disease and cadmium and has suggested that the use of galvanized pipes to carry soft water, common many years ago, caused increased cadmium ingestion. On the other hand, workers exposed to cadmium were reported[55] not to have had a higher prevalence of hypertension than other groups.

No definitive relationship between cadmium levels in the kidney and cardiovascular disease has been demonstrated. For example, Morgan[86] determined the cadmium content of liver and kidney tissue from 80 individuals at autopsy and found no significant difference between controls and hypertensives. Also, no significant difference in the Cd/Zn ratio was found. Szadkowski et al[87] measured the excretion of cadmium in the urine and did not find any correlation with hypertension in a large series of individuals. On the other hand, Schroeder[84] reported that the ashed kidneys of a group of hypertensive US patients contained a mean of 4,220 ppm of cadmium whereas a group of ashed kidneys from presumably normotensive US people killed in accidents contained a mean of only 2,940 ppm of cadmium. In a later report,[88] but without additional information, Schroeder reiterated his belief that people dying of cardiovascular diseases have higher concentrations of cadmium in their kidneys than normotensive ones.

(f) Skeletal Effects

(1) Bone

Nicaud and associates[38] described a group of storage-battery workers exposed to cadmium oxide dust who had symptoms of back and extremity pain and difficulty in walking. Isolated cases of bone changes have also been reported in British cadmium workers.[34,71] In some of the workers described by Nicaud et al,[38] pseudofractures were noted on X-ray examination of the scapula, pelvis, femur, and tibia. The causes of these bone changes, similar or identical to those of osteomalacia, are not known. It may be that altered tubular function, with impaired renal tubular regulation of calcium/phosphorus balance, is primarily responsible for bone demineralization, as suggested by Friberg and associates.[1] (p 121) But other factors, such as decreased gastrointestinal absorption of minerals, changes in Vitamin D activity, or changes in parathyroid activity or other hormonal effects have not been ruled out.

The Itai-Itai ("ouch-ouch") disease which occurred in certain areas of Japan was attributed to pollution of water and crops by industrial, cadmium-containing waste.[1] (pp 137-161),7,40,41,89 The disease is apparently osteomalacia and involves painful joints and bones, especially in the back and legs. Those affected were mostly multiparous, postmenopausal women. A nutritionally deficient (low calcium and protein) diet was perhaps an additional factor. Low estrogen levels may also have had some bearing on the osteoporosis seen in these cases.

(2) Teeth

The development of a yellow ring at the neck of the tooth was reported in early epidemiologic surveys in occupationally exposed persons and was at one time suggested to be a warning sign of chronic cadmium intoxication.[62,90] Whether this is because of surface absorption of cadmium, reaction with

salivary sulfur-containing substances, or through metabolism has not been established.

(g) Liver Effects

Friberg[55] reported abnormal liver function tests in workers exposed to cadmium oxide dust for a mean exposure time of 20 years in addition to kidney changes and emphysema discussed earlier. Other investigators[34,54] have commented that in contrast to the frequent, pronounced changes in renal function, gross changes in liver function are unusual findings in cadmium-exposed workers. It is not known at present to what extent liver abnormalities occur in workers exposed for long periods.

(h) Gonadal Effects

Little attention had been drawn to the effects of cadmium on gonads prior to the mid-1950's when Parizek[91] and Parizek and Zahor[92] described the destructive effects on testicular tissue in animals, since confirmed by others in testicular or ovarian tissues in several species of animals (see later discussion in *Animal Toxicity*). Favino and coworkers,[93] in their studies of fertility of 10 cadmium workers, revealed one case of impotency; abnormally low testosterone blood levels were found only in this man. Smith et al[94] found high levels of cadmium in the testes of men exposed to cadmium fume. They also reported microscopic changes (depression of maturation) in the testes at autopsy, but, because of the relatively small mitotic activity of spermatocytes, they ascribed this depression to terminal illness. Further studies are necessary before any final conclusion can be drawn concerning the possible effects of cadmium on gonadal function in persons exposed to cadmium. It should be noted that the data on gonadal changes developed in animals were all obtained from acute animal experiments, and corresponding doses in man would represent an unusually high, conceivably lethal, exposure.

(i) Teratology

The question of teratogenicity of cadmium has not been thoroughly examined in man but has been investigated experimentally in animals (see discussion on *Animal Toxicity*). Tsvetkova[95] reported that children born of women occupationally exposed to cadmium at high concentrations weighed less than children of a group of women considered to be unexposed controls. There were only 20 controls, and no mention was made of whether consideration was given to other possible determinants of birth weight, such as maternal weight, number of previous pregnancies, socioeconomic conditions, prenatal nutrition, maternal illnesses, and smoking habits. Four of the children born to these cadmium workers had signs of rickets, one had retarded eruption of teeth, and two had undescribed dental troubles. Piscator (written communication, December 1975) has interpreted these changes as the result of fetal zinc deficiency as the consequence of zinc retention by the cadmium-exposed mothers. This point has been discussed in more detail by Friberg and coauthors,[1 (p 129)] who have suggested, in a review of reproductive changes in experimental animals, that teratogenic effects are the consequence of this zinc deficiency in the fetus because of zinc retention by the mother.

(j) Carcinogenesis

Surveys of cadmium workers have indicated that carcinoma of the prostate may be found more frequently in these men than in the general population.[65,96] Prostatic cancer was cited as the cause of 3 of 8 deaths in a survey by Potts[65] of 74 men with more than 10 years exposure in a nickel-cadmium battery factory. Kipling and Waterhouse[96] surveyed a group of 248 workers exposed to cadmium oxide for a minimum of one year. There were 4 deaths from prostate cancer, significantly more than expected. Cancer rates of the bronchus, of the bladder, of the testis, as well as cancer rates at all sites, were not significantly different from the expected rates. According to a communication from Kipling to the International Agency for Research on Cancer (IARC),[4] 3 of these cases of prostate cancer were also 3 of Potts' cases.[65] Kipling and Waterhouse cautioned against drawing conclusions until further studies had been undertaken. They indicated that inquiries of cadmium users had been initiated and that ". . . so far [these] have proved negative . . ." but gave no details.

Adams et al,[71] in a study of the same plant previously described by Potts,[65] reported two cases of prostate cancer among 12 deaths occurring during the 12-year period of study. One prostate cancer death was clearly not in the group reported by Potts, but the other case may also have been one of Potts' cases. Discrepancies in specific details about this plant in the two studies make close comparison of their data impractical.

Lemen et al[97] studied causes of death in 92 workers, from a cohort of 292 in a cadmium smelter,

who had died during the period 1940-1974. Four cases of prostate cancer were found, compared to 1.15 expected on the basis of mortality rates for the US white male population adjusted for age and calendar year. One case was a 64-year old worker who died in 1951; all others were 71 years of age or older. When only those workers who had lived for at least 20 years after their first exposures to cadmium were considered, 0.88 deaths would have been expected vs the 4 observed. The difference between these two figures was said to be significant at the 0.05 level whereas that between the 1.15 deaths expected in the entire cohort and the 4 observed was not significant. These employees were also exposed to arsenic at low concentrations, as is discussed later in *Epidemiologic Studies*.

These studies[65,71,96,97] suggest that occupational exposure to cadmium oxide may increase the risk of prostate cancer in man, but the numbers of men developing prostate cancer were small. In addition, as mentioned above, two, and possibly three, of these studies are not independent ones.

Of the 74 men exposed for 10 or more years at various concentrations of cadmium oxide dust in the production of alkaline batteries reported by Potts[65] in 1965, 8 died. Three of these deaths resulted from carcinoma of the prostate, one from carcinoma of the bronchus, and one from carcinomatosis. Details of the post-mortem examination or the bases for diagnosis of prostate cancer were not given. The age range of these men (65-75) is probably relevant, also.

In 1949, concentrations of cadmium in the air of plate-making and assembly shops ranged from 0.6 to 2.8 mg/cu m, and in the electrode department concentrations as high as 236 mg/cu m were reported. Installation of local exhaust ventilation in 1950 reduced concentrations below 0.5 mg/cu m in most parts of the factory. In 1956, further major improvements reduced levels to 0.1 mg/cu m at most points.

Lemen et al[97] also found a significant excess of malignant tumors of the respiratory tract (12 cases observed compared to 5.11 expected). Eight of these were characterized histologically; one was an undifferentiated small-cell tumor, three were anaplastic, three were squamous-cell carcinomas, and one was an oat-cell carcinoma. While a more local comparison group might have been better, the excess mortality due to lung cancer among the people exposed to cadmium probably would not have been decreased by this procedure. The authors also noted a significant excess in total neoplasms (27 observed vs 17.51 expected).

No excess of any form of cancer was detected in 3 other studies[1 (p 132),98,99] of men occupationally exposed to cadmium, but sample size of each study was small.

A geographical correlation between the frequency of prostate cancer and the amount of suspended particulate air pollution in various communities was reported in 1969 by Winkelstein and Kantor[100] with the suggestion by the authors that cadmium exposure might be involved in the association, but measurements of cadmium in the ambient air were not performed. Smoking histories and socioeconomic factors might also be relevant in evaluating any such association.

In an epidemiologic study of cancer in persons exposed to cadmium, Kolonel[101] compared the incidences of several types of cancer in persons having an inferred occupational history of cadmium work with those in a control population. The basis for inferring a history of occupational exposure to cadmium was indirect, from job classification information revealed in an interview on admission to a cancer research hospital. The test and control populations were all white males, aged 50-79 years, and were all referred to the Roswell Park Memorial Hospital in Buffalo, New York, because of suspected neoplastic disease. One group of controls were those found to have nonneoplastic gastrointestinal disease; a second group of controls were those found to have colon cancer. Kolonel found a significant increase in renal cancer, and a nonsignificant increase in pancreatic cancer among the patients thought to have been exposed to cadmium. He anticipated an increased incidence of prostatic cancer, but found none. He looked for a similar increase in cancer among those exposed to cadmium from dietary intake of cadmium or from smoking, but the association was questionable. In view of the deficiencies in his data on occupational histories, conclusions from this study are uncertain.

In a later publication based on these data, Kolonel[102] commented on evidence of a synergistic relationship between exposure to cadmium and cigarette smoking. In the belief that the greater than additive effect could not be accounted for by the increased cadmium exposure, he suggested that some other component of cigarette smoke

contributed to the synergistic effect. However, in addition to the uncertain evidence commented on above on occupational exposure of the subjects to cadmium, his assumptions about exposure concentrations may have been inaccurate.

In a 1969 letter to the editor of The Lancet, Holden[98] mentioned having studied 42 cadmium workers exposed 2-40 years, 6 of them for more than 10 years, at concentrations of cadmium greater than 4 mg/cu m and the rest exposed at an average concentration of 0.1 mg/cu m. There had been one case of carcinoma of the prostate and one of carcinoma of the bronchus in the group. The point of his letter seemed to be to refute suggestions of hypertension among cadmium workers. Although some of the men had proteinuria and emphysema, none of them had a blood pressure greater than 140/90 mm Hg, including a man of 73 years. He also commented that "none is apparently sterile" and that there was no increased incidence of coronary artery disease. Unfortunately, no details were given in this short communication. It is inferred that he was discussing the same population he previously commented on in a 1965 report[59] of men working in a factory making cadmium-copper alloys for trolley wires.

It has been found by Morgan[103] that the cadmium concentrations in blood and tissues were significantly increased in some patients with bronchogenic carcinoma but, as the author commented, whether this elevated cadmium level was the cause or the consequence of the cancer, or was unrelated thereto, is not known. It is possible that the elevated cadmium concentrations and lung cancer were both related to smoking, cigarette smoke usually containing higher cadmium concentrations than the ambient air.

Malcolm,[104] however, came to the conclusion that cadmium is unlikely to be a cause of prostate carcinoma, even though the data available in 1972 suggested this possibility. Malcolm reviewed some then unpublished experiments on rodents conducted at a British cancer research institute and concluded that cadmium is unlikely to be a cause of prostatic or other internal cancer in man. These animal experiments have subsequently been reported by Levy and associates[105-107] and are reviewed in the section on *Animal Toxicity*.

(k) Other Effects of Cadmium

Acute symptoms have occurred in subjects eating cadmium-contaminated food or beverage, according to a review by Fairhall[37] and a report by Lufkin and Hodges.[108] Gastrointestinal manifestations characteristically occurred ¼ to 5 hours after ingestion and were often marked by increased salivation, nausea and vomiting, abdominal pain, diarrhea, and tenesmus. Cadmium has also caused food poisoning from the use of a cadmium-plated refrigerator shelf as a grill to hold steak over charcoal for broiling.[109] A 2-year old child with encephalopathy originally attributed to lead was found to have a very high cadmium concentration of 710 μg/liter in his urine. It was found that the child was fond of licking freshly polished white shoes (polish solution containing 275 μg Cd/100 ml), occasionally ate silver polish (185 μg/100 ml), and ate red paint (500 mg/100 g) from his crib.[110]

Bui et al[111] analyzed the chromosomes in lymphocytes from Swedish battery-factory workers and Itai-Itai patients from Japan, together with controls from Sweden and Japan, and found no significant differences in chromosomal aberrations between cadmium-exposed people and their respective controls. However, sizes of populations studied were small in each case. Mean frequencies of aberrations ranged from 2.0% in Swedish battery workers to 6.7% in Itai-Itai patients. Shiraishi and coworkers[112,113] cultured cadmium sulfide with human leukocyte cells and examined leukocyte chromosomes from 7 Itai-Itai patients, and in each case found an increased incidence of chromosomal aberrations over controls. The rate of abnormalities in the Itai-Itai patients[112] ranged from 14 to 64% of the 50 cells examined, much higher than the rate found by Bui et al.[111] In view of the possible variety of etiologic factors in Itai-Itai disease and the lack of confirmation of the results of a procedure as methodologically delicate as karyotyping, it is difficult to assess these results until additional studies have been conducted. DeKnudt and Leonard[114] found an increased incidence of aberrations in chromosomes cultured from leucocytes of workers exposed to cadmium, lead, and zinc. These changes consisted of chromatid changes (gaps, breaks, deletions, and exchanges) and chromosome anomalies (gaps, fragments, disturbances of spiralization, translocations, centric rings, and dicentrics), usually with only one structural aberration in each abnormal metaphase. The 35 workers, aged 19-58 years, were divided into two groups according to type

and duration of exposure. The first group, consisting of 23 workers, had been exposed to high concentrations of lead and of cadmium for an average of 12 years; the second group, consisting of 12 workers, worked in a rolling mill for an average of 11 years and were exposed mostly to zinc, but with exposures to lower concentrations of lead and cadmium, also. The two exposed groups had statistically significantly higher incidences of anomalies than controls, but the two exposed groups did not differ significantly from each other. As the authors commented, there are inherent difficulties in interpreting studies of such mixed exposures. They noted that seven of the workers in the first exposed group had previously worked in coal mines and that these workers had a rate of severe aberrations (1.35%) nearly twice that of the other members of the same group (0.71%).

There has been some interest in pancreatic function, since high concentrations of cadmium have been found in the pancreata of autopsied cadmium workers.[94,115] Little investigation, however, has been conducted in this field (see *Animal Toxicity*).

High cadmium levels have also been found in thyroids from autopsy material.[115]

Vorob'yeva[116] studied changes in the chronaxies of cutaneous sensory and optical nerves and skeletal muscle in 160 workers exposed to cadmium oxide and compared the results with what she described as normal values cited in the literature and with standards established from studies of 70 workers in contact with otherwise undescribed toxic substances. There had been complaints of headache, dizziness, irritability, depression, and sleep disturbances. Cadmium concentrations in the workroom air varied from 0.1 to 24 mg/cu m, but sampling and analytical methods were not described. The type of industrial operation or other information on possible contributions to observed reactions by other contaminants was not discussed. There was a prolongation of the chronaxy of cutaneous nerves in many cases as well as in optical chronaxy; the changes were proportional to the years of exposure to cadmium. Motor chronaxy changes in 37 workers were variable; in workers with less than 5 years of work experience, muscle chronaxy was reduced, while in workers with 5 years or more of exposure to cadmium, it was increased. Vorob'yeva concluded that cadmium exposure caused central nervous system changes, but suggested the need for further research to resolve questions about the effect of cadmium oxide on the brain. She commented that the changes in the functional state of the cerebral cortex occurred significantly earlier than other signs of cadmium poisoning, but did not describe what signs of poisoning were being compared and gave no supporting data. She presented no actual evidence of effects on the central nervous system. It is not clear how to assess the significance of these findings to a recommended standard for cadmium.

Cigarette tobacco has been reported[117] to contain considerable cadmium (about 30-40 μg/20 cigarettes), about 30% of which is trapped in the filter or remains in the cigarette residual. Approximately 2-2.4 μg/20 cigarettes is inhaled.[33] Approximately 70% escapes into the smoke.[117] Lewis and colleagues[118] found that, of the cases studied, those who died with a diagnosis of bronchitis or emphysema or both had elevated liver cadmium concentrations. Unfortunately, data were not available in this study on occupation or history of cigarette smoking. Another study[103] has reported increased cadmium levels in serum, liver, and kidneys of patients dying with bronchogenic carcinoma.

In a study[119] of 5 people, it was possible to establish that the urinary route of excretion predominates markedly over the gastrointestinal route. Five people were given oral doses of ^{115}Cd-labeled cadmium nitrate, and the radioactivity in urine and feces was followed for 47 days. Urinary excretion of cadmium has been reported in a number of studies.[87,120,121] These studies indicate that the daily urinary excretion in the general adult population is approximately 1-2 μg. Even if fecal excretion also were 1-2 μg, total daily excretion would probably be somewhat less than daily assimilation from food, water, air, and cigarettes, in the case of smokers. This is consistent with the indications from autopsy data that for most of their lives people are not in cadmium balance.[1 (pp 59-65)]

The urinary excretion of cadmium increases markedly with the onset of proteinuria in high cadmium exposure.[71] This is consistent with animal data.[122,123] In man, the magnitude of increased excretion of cadmium in association with proteinuria is quite variable, but may be more than 100 times normal.[71,124] This probably represents an actual mobilization of cadmium stores in the kidney

(and possibly elsewhere in the body), since the kidney cadmium concentration of exposed workers with renal damage is appreciably lower than the concentration in exposed workers who do not have renal damage.[1 (pp 107-08), 34,94]

Epidemiologic Studies

One of the earliest attempts in the United States to study the effects of continued exposure to cadmium in industrial workers was made by Hardy and Skinner[81] in 1947. They reported the clinical histories of five men (ages 28-53) engaged 4-8 years in the manufacture of cadmium-faced bearings. Atmospheric cadmium fume concentrations in the workplace ranged from 0.06 to 0.68 mg/cu m. Cadmium concentrations in urines studied on one occasion were less than 50 μg/liter in all cases. Symptoms reported by these men were varying degrees of fatigue, gastrointestinal upset, and respiratory problems, eg, coughing, sternal pain, and throat irritation, especially on damp days. Four of the five men who claimed to have had good teeth prior to employment had developed dental caries. Two cases had reduced concentrations of blood hemoglobin (70% on Sahli scale). In all five men routine X-ray and urinalysis were normal. The authors suggested that the reported symptoms were due to prolonged cadmium exposure.

Princi[62] studied 20 cadmium smelter workers exposed at atmospheric concentrations of cadmium fumes varying from 0.2 to 6.6 mg/cu m and cadmium dusts (mainly CdS) ranging from 0.04 to 19.0 mg/cu m, in one case as high as 31.3 mg/cu m for 2-3 hours/day. Exposure times varied from 6 months to 22 years (median 4.5 years). Princi noted that personal protective measures were not adhered to. The workers were examined at monthly intervals for three months. The most characteristic finding was a yellow ring at the base of the teeth in 9 of 15 men with natural teeth. From the data presented, degree and extent of coloration did not seem to be related to exposure time, except that the yellow ring did occur more frequently in workers exposed for more than two years. Hematologic tests revealed no significant changes, although the author stated that the hemoglobin and red blood cell counts were slightly lower than expected for that altitude (Colorado, about 5,300 feet). Princi found no evidence of a significant increase above normal of chest complaints; X-ray examinations disclosed no pneumonitis, pulmonary fibrosis, or skeletal changes in long bones. Absorption of cadmium was demonstrated in most cases by levels of blood cadmium (10-40 μg/100 g) and urinary cadmium (25-125 μg/liter). No correlation could be found between blood and urinary values or time of exposure. Renal studies were not reported, although the author mentioned that there were no complaints of genitourinary dysfunction. He found no proteinuria, but his method of detecting protein (boiling test), according to a later communication discussed by Friberg et al,[1 (p 103)] probably would not have detected cadmium-induced proteinuria.

Lemen et al[97] studied the mortality experience between 1940 and 1974 in the same plant studied by Princi.[62] In this later report, the plant was described as producing cadmium metal of high purity by electrolysis followed by melting and distillation in the absence of oxygen. Cadmium oxide was produced by melting the metal in the presence of oxygen and capturing the fume. Cadmium sulfide was produced intermittently by dissolving the metal in sulfuric acid and passing hydrogen sulfide through the filtrate. Princi[62] had previously found environmental concentrations of cadmium fume of from 0.04 to 6.6 mg/cu m and of cadmium dust of 17.23 mg/cu m, with one man being exposed for several hours/day at a concentration of 31.3 mg/cu m. An industrial hygiene survey in 1973 reported by Lemen et al[97] found that most air samples contained less than 1 mg/cu m of cadmium, but some samples ranged up to 24 mg/cu m. Two samples in one department contained 74.8-90.3 μg/cu m of cadmium and 0.3-1.1 μg/cu m of arsenic. A sample taken in another department showed 1.1 mg/cu m of cadmium and 1.4 μg/cu m of arsenic. Prior to initial roasting, bulk samples of preprocessed ore contained 70% cadmium, 6% zinc, 4.3% lead, and 0.3% arsenic; after initial roasting the calcined ore contained 42.2% cadmium, 3.53% zinc, 0% lead, and 0.02% arsenic. Further refining steps reduced impurities further, so that exposure to metals other than cadmium was "considered insignificant." Since a respirator program was in effect, worker exposures were probably less than would be expected from the environmental levels reported. The authors reviewed the mortality experience of a group of 292 white male workers, comparing it with corresponding age-calendar year

statistics for the US white male population. As was discussed in *Effects on Humans*, there was an excess of total malignant neoplasms (27 observed vs 17.51 expected), respiratory system tumors (12 vs 5.11), and prostate tumors (4 vs 1.15 for the entire cohort and 4 vs 0.88 for those who had lived for at least 20 years after their first exposure to cadmium). In addition, there was a nonsignificant excess of deaths from nonmalignant respiratory disease (8 vs 5.04) but a significant decrease in deaths from heart disease (24 vs 43.52), not accounted for by the excess in neoplasms. Total deaths (92) were slightly less than expected (99.32).

In 1950, Friberg[55] reported a comprehensive investigation of 58 workers in a Swedish nickel-cadmium battery factory. The workers were divided into two groups based on their periods of employment. He compared 43 workers (Group I) employed for an average of 20 years, ranging from 9 to 34 years, with 15 workers (Group II) who had worked an average of 2 years, varying from 1 to 4 years. Mean age of workers in Group I was 44 (30-74) as compared to 35 (25-57) in Group II. For controls, Friberg studied age-matched groups of sawmill workers, ie, workers not exposed to cadmium. In the battery factory, the workers were exposed to cadmium (CdO), iron, nickel, and graphite dusts. Air analysis performed at the start of the investigation in 1946 (prior to technical improvements) was considered representative of the workers' exposure in prior years. The amount of cadmium in the dust ranged from 3 to 15 mg/cu m, and 95% of the cadmium-iron dust consisted of particles of less than 5 μm. After protective measures had been installed, factory air analyses (1947, 1948) showed decreased cadmium concentrations (0.2-1.9 mg/cu m) in various plant areas.

The men in Group I complained of more fatigue, shortness of breath, coughing, impaired sense of smell, and sensations of dryness in the mouth than did those in Group II. On examination, 16 of the 43 workers (37%) in Group I had impaired olfactory sense (14 had total anosmia) vs 1 of 15 (6%) in Group II. No correlation of anosmia with atrophic changes in the nasal mucous membranes was found. Atrophic changes were observed in 10 out of 19 cases examined. Of these 10 cases, 6 had anosmia while 4 had normal olfactory sense. Mean values for respiratory function tests (ie, spirometric examination of various lung volume fractions and ventilation ratios) for both Groups I and II were not significantly different from the means of the control groups except for, in Group I, a significant increase in residual capacity and residual quotient and a possibly significant decrease in vital capacity. Considering individual differences, Friberg observed a significant increase in the residual quotients (residual capacity/total capacity) of 12 out of 42 workers (29%) in Group I when compared to matched controls. He considered the increased residual quotient in these cases to be "chiefly caused by a pulmonary emphysema, in the absence of other conceivable causes." In discussing etiologic aspects, he pointed out the possibility that exposure of the battery workers to the other substances found in factory air analyses, particularly nickel, may have contributed to the pulmonary emphysema. His experiments on rabbits demonstrated to him that both cadmium-iron dust and nickel-graphite dust may give rise to emphysematous lung changes, although more pronounced with much smaller concentrations of cadmium in comparison with nickel.

Examination of men in Groups I and II for cardiovascular function based on blood pressure, heart X-ray, and electrocardiogram demonstrated no significant differences from their age-matched controls. Renal function tests carried out in 18 workers of Group I showed a reduction in average urine concentrating capacity (in 9 cases urine specific gravity was 1.019 or less) and a decrease in average inulin clearance (90.3 $\pm$ 5.6 ml/min) as compared to normal values (124.1 $\pm$ 2.2 ml/min) in Swedish males. Precipitation tests with trichloroacetic acid for urinary protein gave positive results in 35 of the 43 workers (81%) in Group I vs 0% in Group II. Further examination of the urinary protein by electrophoretic mobility (9 cases) and ultracentrifugal analysis (2 cases) demonstrated a protein component with lower mobility and molecular weight (20,000-30,000) than ordinary urinary proteins. In this study, proteinuria was found only in the group of workers employed for longer than 9 years (average 20 years). There was a tendency for the renal function tests to correlate with proteinuria. In 12 cases (23%) with relatively persistent proteinuria, the inulin clearance and urine concentration tests showed the lowest mean values. Friberg,[55] however, was not then of the opinion that proteinuria is a result of kidney injury, but rather suggested the possibili-

ty that the kidney injury was secondary to the excretion of the protein component. On examination of the workers' medical records since their time of employment, Friberg found that 8 of the 43 workers in Group I had a history of proteinuria and 5 others were treated for kidney stones. In contrast, none of the workers in Group II had a history of proteinuria and only one had occasionally had pains described as resembling those from kidney stones.

Hematologic tests revealed slightly lower mean values for hemoglobin (86 vs 92) and red cell counts (4.6 vs 5.0) for Group I compared to Group II. However, this could be due to the difference in mean age between the groups (44 vs 35). The average erythrocyte sedimentation rate was moderately increased in both groups, being more marked in Group I (23.5 mm/hour) than in Group II (14.3 mm/hour). Dental changes consisting of a yellow coloring at the base of the teeth, similar to those found by Princi[62] and Barthelemy and Moline, [90] were observed in 12 of 37 workers with natural teeth in both groups and could not be correlated with the use of nicotine. Consistent with Princi's findings, [62] no skeletal changes of the type described by Nicaud et al[38] were found on X-ray examination. Bicycle ergometer testing showed lower working capacity in both Group I and Group II, compared with age-matched controls, but Friberg considered the differences in Group II to be insignificant, whereas Group I results seemed to correlate with higher residual quotients found in pulmonary tests, and on this basis were consistent with "lung changes in the form of an emphysema."

This important study demonstrated the ability of cadmium to cause renal damage and emphysema. It also pointed the way to subsequent proof of the importance of low molecular weight proteins in the urine in detecting effects of cadmium in humans.

Baader[125] reported that 8 of 11 battery workers exposed to cadmium had partial or complete loss of sense of smell. Six of the eight had low molecular weight protein in their urines. Ten of the 11 workers had emphysema. Two had warts, one in the nostril, the other in the epiglottis. Baader[58] commented that women workers were more sensitive to cadmium exposure than male workers, and that blond women were especially sensitive. He gave no details or supporting data, other than to comment that blond women were susceptible to vomiting and fainting, from which one might question whether inhalation of cadmium compounds was the cause.

Bonnell[34] examined 100 workers exposed to cadmium oxide fumes and 104 controls with similar age distribution in 2 British copper-cadmium alloy factories. Nineteen of the 100 exposed workers had emphysema, proteinuria, or both, while 3 of the control group had either emphysema or proteinuria. All 19 men with signs and symptoms had been exposed to cadmium for more than 5 years and 13 of them for more than 15 years. Four additional workers required hospitalization because of shortness of breath. Significant differences in results from certain respiratory function tests were found by Kazantzis[126] between the exposed and the control groups in these same factories, particularly in the time constant of the expiratory forced vital capacity curve. In the group of these workers exposed to cadmium for more than 10 years, Buxton[127] found that the volume of residual air and the residual quotient (ie, residual air as expressed as a percentage of the total lung volume) were both significantly increased. This finding is consistent with Friberg's.[55] The same two factories were reexamined 4 years later in 1957,[72] and 83 of the original 100 men were still working. An additional 24 workers with emphysema or proteinuria, or both, were found, making a total of 43 (43%).

King[128] conducted environmental surveys of these same two plants. Area samples were filtered on dextrose pads and analyzed polarographically after treatment by hydrochloric acid to separate cadmium from copper. Particle sizes in all samples tested were mostly less than 0.5 μm by weight analysis. Air cadmium concentrations in one factory 8 feet from the furnaces varied from 13 to 89 μg/cu m, and in the other 18 feet from the furnaces they were 4-132 μg/cu m in one shop and 1-270 μg/cu m in another shop.

In addition, there were undoubtedly exposures at much higher concentrations, based on the occasional presence of visible emissions of brown (CdO) fumes. King felt that because of variations in concentrations observed and because of significant improvements in ventilation introduced before his survey it was not possible to draw a valid relationship between concentration and disease incidence.

Smith and coworkers[129] in 1955, Potts[65] in 1965, Adams and Crabtree[78] in 1961, and Adams and associates[71] in 1969 have reported successive studies in one factory (originally two factories) where nickel-cadmium storage batteries had been manufactured under the same medical supervision since 1934. In the present factory, annual medical and regular environmental evaluations have been carried on since 1957. Smith et al[129] developed a method for the quantitative measurement of cadmium in urine in order to study the relationship between cadmium excretion and proteinuria in these factory workers. A total of 120 employees exposed to cadmium oxide dust were compared to a control group of 100 workers of similar age without any known cadmium exposure. Proteinuria was observed in 20% of the exposed workers as compared with 5% of the control group. The normal range of urinary cadmium was found to be 0-20 μg/liter, while the range in workers exposed to cadmium was 10-580 μg/liter. Proteinuria did not appear to be related to urinary cadmium. Potts[65] reported 44% of 70 men (aged 37-73) with over 10 years (maximum 40 years) of cadmium exposure to have proteinuria, and 64% to have some degree of anosmia. Apart from proteinuria, there was no evidence of renal damage by clinical examination of two workers or post-mortem examination of two men who had proteinuria for many years. He investigated deaths of past workers and found 8 deaths out of 74 men with at least 10 years' exposure. Five of these deaths were from cancer, of which three were prostatic (discussed earlier in *Effects on Humans*). However, the source of information as to the cause of death was not stated (ie, whether from a post-mortem examination or the death certificate). Adams et al[71] found that 14 of 100 men then working had proteinuria, and 14 of 100 had anosmia (five with proteinuria). Although the average FEV_1 for the group was significantly reduced (p less than 0.001) from normal, 22 of 27 men examined were within normal range. In a previous study by Adams and Crabtree[78] in 1961, the incidence of proteinuria was 17 of 106 exposed workers, indicating minor change over the years. Air samples taken at regular intervals and analyzed for cadmium in the years 1957-1967 showed concentrations that ranged from 0.05 to 0.5 mg/cu m in assembly areas, 0.05 to 1.0 mg/cu m in platemaking areas, and 0.2 to over 5.0 mg/cu m in the negative electrode material department. Marked decreases in airborne cadmium were noted in 1950 and 1956, after which concentrations were fairly stable until 1967, when new facilities for platemaking reduced the airborne cadmium levels in that operation to less than 0.1 mg/cu m.[65] Dust measurements showed approximately 20% to be in the respirable size range.[71]

Kazantzis and colleagues[54] reported on a group of 12 workers employed in making cadmium sulfide pigments (cadmium zinc sulfide or cadmium selenosulfide) and cadmium oxide. Of the 12 workers, 6 had worked 25-31 years with cadmium. Of these 6, all had proteinuria, 3 had mild respiratory symptoms such as breathlessness on exertion, and one had recently died from emphysema. There was some impairment in respiratory function tests, but no abnormal physical signs were detected. The 4 men with 12-14 years' exposure without clinical proteinuria still were excreting protein, electrophoretically similar to that excreted by the men with clinical proteinuria. The urinary protein had a higher than normal amount of globulin components, which was suggestive to the author of nonspecific tubular malfunction, but he also observed some glomerular fibrosis in two kidney biopsies and in one autopsy. Only 3 workers who had been exposed less than 2 years showed no abnormalities. In 4 of the 12 workers, there was increased urinary excretion of calcium and, in 3 of 8 men with proteinuria, there were glycosuria, aminoaciduria, and decreased water reabsorption. The authors found no yellow discoloration of teeth. They found no definite evidence of sterility based on fertility histories. One worker had progressive loss of ability to smell and another had a perforated and ulcerated nasal septum, thought by the authors[54] to be possibly unrelated to cadmium exposures. No environmental measurements were reported.

Ahlmark and associates[76] reported on 110 cadmium-exposed workers and 22 controls. Several test measurements showed that kidney functions were reduced with long exposure. Urinary protein excretion increased regularly with length of exposure from 100 mg/24 hours (ranging from 50 to 170) at less than 5 years to 955 (ranging from 370 to 1800) mg/24 hours at 31 years and over. The incidence of kidney stones increased from 9.1% in the controls to 12.3% in the 6- to 10-year exposed group and to 43.6% in the greater than 15-year ex-

posure group. No environmental measurements were reported from this nickel-cadmium storage battery plant, whose workers had been previously studied by Friberg.[55]

Suzuki and coworkers[61] reported on a polyvinyl chloride-film plant in which lead and cadmium stearates were used as stabilizers. In 1963, 27 exposed and 7 nonexposed workers were examined. The risk due to lead was presumed by the authors to be negligible. Examination of their data largely supports this presumption; urinary coproporphyrin levels were not increased in exposed workers compared with that of controls, and most of the urinary lead levels were below 200 μg/liter. Although airborne lead concentrations were higher than those of cadmium, particle sizes of lead compounds were larger than those of the cadmium stearate. Eight of 17 workers reexamined in 1964 had increases in degree of urinary protein excretion by the trichloracetic acid (TCA) test. The numbers that were positive were significantly greater in the exposed workers than in the controls in the 1964 tests. Statistically, this might possibly have been due in part to the larger number of controls and therefore to a more normal distribution curve which is apparent in the 1964 data (24 controls vs 7 controls in 1963). These increases were demonstrated by all three methods of testing for urinary protein, namely 25% TCA test, sulfosalicylic acid test, and boiling test, with TCA being the most, and boiling the least, sensitive. No significant differences in respiratory function were found between exposed and control groups. No significant differences in mean urinary cadmium levels were demonstrated, though there were a few slightly higher urinary cadmium levels in the exposed group. No differences in olfactory acuity between the two groups were shown. Yellow discoloration of the teeth of exposed workers was looked for but not found. Liver function, as evidenced by the results of thymol turbidity and serum cholesterol tests, was not significantly different in exposed and control groups. Similarly, there were no significant differences in hemoglobin, urine specific gravity, or urine occult blood, but there was a slight increase in urine sugar (by test tape) in exposed workers as opposed to controls. Both groups had less than 0.05% of cells with basophilic stippling. However, the average age of the workers in this study was lower and work experience was less than that of work populations described in US, UK, and European studies. Workroom air was sampled by impingement in 10% nitric acid at a sampling rate of 20 liters/minute. Lead and cadmium in the samples were analyzed by appropriate modifications of dithizone colorimetry. Each work operation, involving exposure to lead stearate and cadmium stearate as well as to organic plasticizers, took 20 minutes to complete and these processes were repeated 3 or 4 times in each 8-hour work shift. Environmental measurements showed 0.03-0.7 mg/cu m cadmium in 1963 and 0.02-0.2 mg/cu m in 1964, but the operations covered only about 1 hour/day. Particle size distributions were studied in several operations, including casting of both lead and cadmium stearates (mixed casting) and of cadmium stearate alone (cadmium casting). These distributions were: 25% in mixed casting and none in cadmium casting in the 6-20 μm range; 17% in mixed and none in cadmium in the 0.7-2 μm range; and 42% in the mixed and 83% in the cadmium casting in the 0.4-0.7 μm range.

Tsuchiya[63] reported on 13 workers (aged 19-32 years) exposed to cadmium fume (probably CdO fume) in a silver and cadmium alloy smelting operation, compared with 13 age-matched nonexposed factory workers. The periods of exposure ranged from 9 months to 12 years. Samples were collected by an electric dust sampler and were analyzed polarographically. One day of air sampling continuously at nose level on each of 5 workers selected for a time study gave TWA's of 68-250 μg/cu m of cadmium, with an overall weighted average exposure for the 5 workers of 125 μg/cu m. While most workers were not exposed for 8 hours/day (about 6 hours/day was common), workweeks were 5-6 days. Both the specific gravity and the concentration of hemoglobin in blood were significantly lower in all cadmium workers than in controls, while urine coproporphyrin levels were higher. Urinary protein levels by quantitative microdetermination were considerably increased in exposed workers except for 3 workers who had only 9 months of exposure. Workers with more than 5 years' exposure had the highest urine protein levels. The cadmium workers excreted 114-667 μg/ml, and the control group 29-82. Similarly, urinary cadmium levels were elevated in exposed workers (35-140 μg/liter) except in the same 3 workers and in 9 controls, whose urinary cadmium levels were all lower than

15 μg/liter. Other than proteinuria and anemia, no abnormalities were noted. These findings are consistent with the impression from reviewing other reports on cadmium toxicity that serious renal effects of cadmium, as presaged by high proteinuria and as evidenced by increased cadmium excretion, develop slowly and with early warning of serious changes.

Tsuchiya[63] concluded that his data argued against the TLV of 0.1 mg/cu m and suggested that a value of about 0.05 mg/cu m would be preferable, at least for Japanese workers.

In 1976, Tsuchiya[130] reported on the same plant he had studied 10 years earlier.[63] Five of the original 13 workers were still employed there; others had left the company and new workers had been employed, with a total of 16 workers being involved in the later study. The working environment had been improved in the interim, except for a period in 1970 when engineering controls did not function properly, and workers had started wearing respirators at least part of the time. Some workers with significant proteinuria in the previous study had been transferred to other operations. Except for two of the original five workers, none had proteinuria by sulfosalicylic or TCA test. Two of these who were not proteinuric by these tests had increased concentrations of β_2-microglobulin in the urine, one slightly and the other moderately increased. One worker who had a severe proteinuria from 1965 to 1970 had been hospitalized in 1970. After discharge from the hospital, he changed jobs and was lost to further examination. A renal biopsy taken in the hospital showed slight microscopic changes in the tubules, with a very slight thickening of Bowman's capsule in the glomeruli; there was no clinically apparent impairment of renal function.

In 1965, environmental concentrations had averaged 125 μg/cu m of cadmium, then had decreased, rising in 1970 to 282 (11-1,116) the first half of the year and 114 (7-586) the second half. Subsequently, environmental concentrations decreased; in 1971 they were 28 (2-118) μg/cu m the first half of the year and 25 (4-65) the second half; in 1972 they were 29 (11-57) the second half (first half-year not being given); and in 1973 they were 16 (7-29) the first half and 16 (9-20) the second half. The improvement during and after 1970 was attributed in part to replacement of the gas furnace with an electric furnace.

The original 5 workers improved during the 10-year period in terms of clinical test results. New workers had not developed proteinuria. Glucosuria was not observed, but the author[130] commented that the paper test method used might have been less sensitive than quantitative methods used by some investigators. All workers in the later study were normal with respect to blood specific gravity, erythrocyte counts, hemoglobin, and hematocrit; this represented an improvement in the case of the older-service workers, suggested to be due in part to improved nutrition and in part to decreased exposure to cadmium. A positive correlation between blood and urine cadmium was not found. Tsuchiya concluded that cadmium-induced proteinuria is reversible in some workers (probably those with proteinuria of short duration).

Tsuji et al[79] studied a number of workers exposed to cadmium in a zinc refinery. About 90% of the workers reported on were male, the rest female. Proteinuria detected by sulfosalicylic acid occurred in 14.7% of the men and 15.5% of the women. Analysis of sugar in urine by a test tape showed positive results in 7.8% of the men and 1.4% of the women. There were some complaints of respiratory tract symptoms, nasal symptoms including anosmia, weight loss, and nocturnal pollakiuria. Many examinees had a history of stomach or duodenal ulcers. Yellow rings on the teeth were looked for but not found, but the authors commented that stained teeth, poor dental repair, and ill-fitting dentures made the examination of questionable significance. Environmental data were not reported. If men and women were similarly distributed between the various types of exposure, an inference that the sexes were not different in their sensitivity to cadmium would be reasonable; however, it is not clear whether men and women were so distributed.

Tsvetkova[95] investigated whether cadmium affects reproduction. She examined 106 women, aged 18-48, who had spent 2-16 years in work involving cadmium exposure. Some of these workers were exposed to cadmium oxide at concentrations stated to be 0.1-25 mg/cu m, some in a chemical factory involving exposure to soluble cadmium salts at 0.16-35 mg/cu m, and some in a zinc-casting factory where cadmium sulfate, cadmium sulfide, and metallic cadmium were present in a concentration of 0.02-25 mg/cu m. Sampling and analytical procedures were not described. Tsvet-

kova was unable to show changes in the menstrual cycles of women exposed to cadmium as compared to unexposed women serving as controls. There were isolated menstrual changes but these were attributed to endocrinal-gynecologic illness which, however, the author[95] attributed to working with cadmium. Courses and times of pregnancies were normal. However, children born to these cadmium-exposed women weighed less than children of control workers. Four of the children born to cadmium-exposed women had signs of rickets, one had retarded eruption of teeth, and two had dental disease otherwise undescribed. These changes were not present in children of control workers. Details of findings and bases for conclusions were not presented. Most of the paper was concerned with the effects of cadmium on reproduction in rats, described later under *Animal Toxicity*. At the concentrations to which these women were exposed, renal changes might be expected as well as renal complications of pregnancies, but Tsvetkova did not comment on these points.

Piscator et al[131] studied 53 women, aged 18-71, all but four of whom worked in a cadmium-nickel battery factory previously studied by Friberg,[55] who had found renal and lung damage in male workers approximately 25 years previously; two of the women then worked in another factory, and two were retired. The control group consisted of 34 women, aged 18-60, who worked in a candle factory in the same city as the battery factory; these women had no known exposure to metals. The exposed and control groups were fairly well age-matched except that there were no controls over 60 years of age; 5 of the exposed group were 60-71 years old. Air concentrations, said to be below 100 but mostly about 40 μg Cd/cu m, based on personal sampling, were considerably less than the concentrations at which the previously studied men had been exposed (M Piscator, written communication, October 1975). Sedimentation rates, blood hemoglobin, 26 serum constituents, and various urine components including total protein and β_2-microglobulin were studied in these workers. In the age group 50-59, there was a statistically insignificant increase in hypertension in exposed women. There was a significant increase in average haptoglobin and sedimentation rate in the 40-49 age group and a nonsignificant increase in the 18-29 year age group. Serum iron was lower in the 50-59 year group. There were no significant differences in urinary findings. Among the controls there was one case with a very high excretion of β_2-microglobulin; the pattern obtained by electrophoresis of urine suggested an effect on tubular function but there was no glucose in the urine, and a bacterial infection involving the tubules was suggested as the explanation. There was a slight tubular dysfunction in a 71-year-old exposed woman, but without increased β_2-microglobulin excretion. She had been classified as a suspect case in 1969.

Piscator et al[131] also observed significant differences in blood and urine cadmium, and found that urine cadmium, but not blood cadmium, increased with age. They also noted a slight decrease in urine zinc with exposure time, except that urine zinc was increased by use of drugs for treatment of hypertension. Smokers had significantly higher blood cadmium levels than nonsmokers; differences between cadmium-exposed smokers and nonsmokers were not found in urinary excretion of cadmium but control smokers excreted more cadmium than control nonsmokers. It was believed that cadmium might have been deposited on cigarettes during work, then vaporized during smoking and inhaled. They found a significant correlation between blood and urine cadmium in nonsmokers exposed less than 10 years but not in smokers.

Kjellstrom and associates[132] studied the excretion of β_2-microglobulin in male and female workers in the battery factory originally studied by Friberg.[55] There were 240 male and female workers exposed to cadmium oxide dust and to nickel hydroxide dust in the study group, and there were 87 unexposed male controls. The exposed workers were employed in the department where materials for battery electrodes were made (material plant) or where the electrodes and batteries were assembled (assembly plant). Stationary and personal samples were collected on millipore filters except in 1959 and prior years and analyzed by atomic absorption spectrophotometry. Particle size analysis in 1972 showed that 95% of the particles were smaller than 5 μm. Environmental concentrations had been occasionally measured in the factory from 1946 on, but systematic measurements based on personal sampling had not been performed. Individual samples in the assembly plant in 1946, based on stationary samplers, averaged 6.8 mg Cd/cu m (range 3-15), were reduced in 1947 to an average of 760 μg/cu m (range 400-1,000),

becoming further reduced gradually to 340 μg/cu m (range 3-2,150) in 1961. Between 1967 and 1972, sample averages ranged from 22 to 91 μg/cu m and individual samples ranged from 6 to 802 μg/cu m. Concentrations of nickel hydroxide were reported to be 2-10 times the cadmium concentrations. In 1968, stationary samplers in the material plant were analyzed and found to contain cadmium equivalent to 7 and 31 μg/cu m; however, personal samples showed airborne concentrations of 10-4,800 μg/cu m (median of 290). In 1972, stationary samplers showed levels of 8-170 μg/cu m and personal samplers showed 280-690 μg/cu m. Exposure concentrations at the time of the study, apparently referring to both plants, were described as about 50 μg/cu m. Protective masks were occasionally but not consistently used by the workers.

Diagnosis of proteinuria was made in those whose microglobulin excretion was greater than the upper 95% confidence limit of the normal concentration in the urine; the authors cautioned that this was not considered necessarily to be a clinically significant proteinuria. There was an increased incidence of microglobulinuria in the exposed group. In the unexposed controls, 3.4% had microglobulinuria. In the assembly plant, women had a 2.3% incidence of this type of proteinuria and men had a 25% incidence. The men who worked in the material plant had a 52% incidence of microglobulinuria. These incidences in male workers were significantly different from control incidences at p less than 0.001; differences in incidences between female workers and controls were not significant. The 2.3% incidence among working women represents one case of microglobulinuria among 41 women. Yet 15 of the women had been exposed for more than 5 years. The authors speculated that the lower rate of microglobulinuria among women might in part reflect a lower smoking rate; of the 13 women whose smoking habits were known, 5 were smokers. Nonsmoking cadmium-exposed workers had a lower prevalence of the defined proteinuria than smoking cadmium-exposed workers. Nine of the workers were separately treated in the study because they were from Yugoslavia, where tubular proteinuria is endemic (Balkan nephropathy); two of them were found to excrete increased amounts of microglobulin. In the 185 employees that worked continuously with cadmium, the prevalence of microglobulinuria increased with exposure time.

Lauwerys and coworkers[133] studied Belgian cadmium workers exposed for periods up to 40 years. They took breathing zone samples of total cadmium particulate and, in the most polluted sites, of respirable cadmium particulate, ie, aerodynamic diameter of less than 5 μm. Samples were analyzed by atomic absorption spectrophotometry. The workers were drawn from 3 different factories, an electronic workshop, a nickel-cadmium storage battery factory, and a plant producing cadmium. Each factory had a control group selected to match the exposed group in sex, age, weight, height, smoking habits, and socioeconomic status. Since no important modifications had occurred in the different industrial processes since their institution, the authors believed that levels of airborne cadmium found in the 3 plants were quite representative of past exposure. A description of the exposed groups and the workroom cadmium levels found are given in Table III-1.

Control groups were described as C1, C2, and C3, corresponding to the three exposed groups. Exposed groups were exposed to dust of cadmium or its compounds; four workers in Group E3 were also intermittently exposed to fume.

In group E1, the only change was a slight increase in urine cadmium; there were no significant differences in pulmonary function indices, but it was noted that an effect of cigarette smoking on pulmonary function was evident.

In group E2, in both smokers and nonsmokers, all pulmonary indices were on the average lower than the corresponding control group, but these differences were not statistically significant. Blood and urine cadmium concentrations were higher than control levels. Electrophoresis showed evidence of glomerular proteins in four workers. One worker known to have glomerulonephritis had what was described as excessive proteinuria.

In group E3, pulmonary indices (FVC, FEV_1, and peak expiratory flow rate) were significantly lowered. Cough but not expectoration was more common in E3 than in C3 workers. There were slight but statistically significant changes in some of the blood enzymes, viz, an increased β-galactosidase, an increased lactic dehydrogenase, and a decreased RBC acetylcholinesterase; hematocrit was also lower in E3 than C3. However, these changes were not sufficient to suggest adverse health effects. There was an abnormal electrophoretic pattern of urinary proteins found in 15

workers in E3. Urinary cadmium was elevated, markedly so in those whose proteinuria was believed to be pathologic. There were slight increases in blood cadmium, also. Of the 15 workers whose urinary proteins showed abnormal electrophoretic patterns, selective glomerular proteinuria was diagnosed, on the basis of electrophoretic pattern, in 7; in the other 8, there was a mixed proteinuria, ie, of the glomerular-tubular type, and this was confirmed by immunoelectrophoresis.

It is interesting that E3 workers, consisting of 22 men exposed 21-40 years, were more markedly affected by exposure at 66 μg/cu m than the E2 workers, consisting of 27 men exposed for less than 20 years at more than twice that concentration (134 μg/cu m), and this suggests the importance of length of exposure, compared to exposure concentration, in the development of chronic toxicity from cadmium. However, some of the E3 workers were also exposed to cadmium fumes, apparently at higher concentrations.

The authors[133] suggested that their data supported a reduction of the environmental limit of cadmium dust to 50 μg/cu m. They also recommended that urine cadmium determinations be performed, and that urinary cadmium should be kept below 15 μg/g of creatinine.

Lauwerys and coworkers[134] also studied a group of 90 workers exposed to cadmium oxide dusts for less than 20 years (average of 7.5 years) and another group of 25 workers exposed for over 20 years (average of 27.5 years). Concentrations at the time of the study were usually below 90 μg/cu m total cadmium dust and below 30 μg/cu m respirable dust. Both groups had slight but significant reductions in pulmonary function, a marked increase in blood and urine cadmium, and kidney lesions diagnosed from electrophoresis of urine protein. The incidence of kidney lesions was 9% in the group with the shorter work experience and 64% in the group with the longer exposure. Exposure caused a higher increase in urine cadmium than in blood cadmium. Their data on blood cadmium suggested that it did not increase with duration of exposure, that it does not reflect body burden of cadmium, but that it may reflect current exposures. They suggested that at low cadmium exposure concentrations urine cadmium might at least partially reflect body burden. They did not find a correlation between cadmium in the urine and duration of exposure with or without kidney lesions.

Further details of these studies[133,134] as well as of those on other workers exposed to cadmium have been published in a comprehensive report, also from the Catholic University of Louvain, Belgium, by Materne et al.[135] Some of these worker groups were also exposed to lead, which may make some of the observations less clearly attributable to cadmium. However, the authors concluded that lead absorption had little or no role in the kidney changes, and that the effects in the kidneys were from cadmium absorption by these workers. In Factory I, involving electronic manufacture, 26 exposed women and 26 control women were studied. There was no lead exposure in this group. In Factory II, where nickel-cadmium batteries were made, 21 exposed male and 6 exposed female workers were studied, with 19 control males and 4 control females. In Factory III, involving cadmium production, 25 exposed and 25 control males were studied. In Factory IV, also involving cadmium production, 66 exposed and 65 control men were studied. Controls were matched with cadmium-exposed workers in age and in smoking habits. Airborne cadmium concentrations were variable, ranging between 7 and 19 μg/cu m in Factory I, 6-94 in Factory II, 1.2-97 in Factory III, and up to several mg/cu m in Factory IV, after omitting several values (eg, 27 mg/cu m) that were believed due to gross contamination of samples. The concentration ranges mentioned were smaller in specific work sites within a factory.

Differences between exposed and control groups were often less remarkable than differences between smokers and nonsmokers. In Factories II and III there were decreases in hematocrit; while this might be attributed to lead, airborne lead concentrations were in the range of 40-50 μg/cu m, which seems unlikely to be high enough to cause anemia, so possibly the reduction in hematocrit was due to cadmium alone or to cadmium and lead.

Another group consisting of 108 exposed and 110 control workers were exposed at 74-210 μg/cu m total (20-30 μg/cu m respirable) cadmium dust, of whom 18 exposed workers had what was described as pathologic urine proteins on electrophoresis. Proteinuria was also seen in some workers in Factories III and IV, together with pulmonary function decreases. The authors concluded that, in order to prevent any renal impairment, airborne cadmium, whether dust or fume, should not exceed 50 μg/cu m.

Animal Toxicity

In the ensuing discussion of animal toxicity, emphasis is given to those investigations which significantly add to information from human studies, eg, reproductive effects and experimental carcinogenesis, with a resultant lack of emphasis on those effects more extensively studied in humans, such as renal and pulmonary effects. In addition, in such areas as testicular effects and biochemical studies, where there are many published studies, the more representative or important studies have been selected for discussion.

(a) Skin

Little is known about the absorption of cadmium through the skin. The only cadmium salt which has been studied in this regard is the chloride, and the only species of animals studied has been the guinea pig.[136,137] An absorption of 1.8%/5 hours was observed when the concentration of aqueous solution applied was 0.239 M. At lower concentrations, the absorption was less than 1%/5 hours. From these data, significant absorption of cadmium through the skin does not seem likely, but more definitive studies are needed.

(b) Blood Effects

Decker et al[138] studied the effects of long-term ingestion of low levels of cadmium in young rats (34 days old). Six groups of rats were given water containing from 0.1 to 50 ppm cadmium chloride; controls received distilled water only. The animals were killed at various intervals up to one year, and blood and tissue samples were then analyzed. A 50% reduction in hemoglobin was found in rats ingesting 50 ppm cadmium for three months. Rats given from 0.1 to 10 ppm cadmium for one year showed no differences from control groups.

Fitzhugh and Meiller,[139] in a study published only as an abstract, reported giving Cd(II) as cadmium chloride (15-135 ppm) to 3-week old rats in their diets for up to six months. There was evidence of toxicity at concentrations of 45, 75, and 135 ppm. At 135 ppm, dietary cadmium caused a marked anemia with hemoglobin values as low as 4 g, and erythrocyte counts of two million in some cases were observed. A reduction in growth weight occurred, and in some instances early death. Some animals on 45 ppm had no blood changes after one year, and only one animal on 15 ppm had marked anemia. Bleaching of the incisor teeth was observed in all animals except in some animals receiving 15 ppm Cd(II).

Oral administration of large doses of an unstated form of cadmium (75 mg/kg) to Japanese quail [140] for four weeks produced severe anemia (hematocrit value reduced about 50%) and growth retardation. Low concentrations of iron with high concentrations of cadmium in the liver were observed. The authors suggested from their data that a primary effect of cadmium under these conditions and in this species was the production of an iron-deficiency anemia, which could be prevented by adequate dietary ascorbic acid. Friberg[55,141] has also suggested that the type of anemia induced by cadmium is mainly hypochromic and microcytic. He studied the effect of iron in male rabbits injected sc with 0.65 mg/kg of Cd(II) daily for 70 days.[141] One group received iron, and another group was given liver three times a week. In animals given iron, the hemoblogin values were significantly higher than the other groups; however, even large amounts of iron did not completely prevent the development of anemia. This observation indicates that the anemia was due in part to an alteration in iron utilization. In this connection, Kench and Gubb[142] reported a study in which chick embryos were injected seven days before hatching with 12-15 μg Cd(II). The livers of the newly hatched chicks were found to have impaired biosynthesis in vivo of catalase, a heme-containing enzyme.

Dalhamn and Friberg[143] administered cadmium sulfate sc to 3 groups of rabbits, 6/group, 6 days/week, for 10 weeks, at 650 μg Cd/kg. Two of the groups were injected thrice daily with dimercaprol, one at 4 and the other at 12 mg/injection; the third group received only cadmium sulfate. Four of the animals on the high dose of dimercaprol and 3 receiving only cadmium sulfate died during the experiment. There was a progressive weight loss in all groups, greatest in high-dose dimercaprol animals. Proteinuria developed in all but two rabbits, earlier in most of the animals receiving the higher dose of dimercaprol. There was a significant and progressive decrease in hemoglobin concentrations in the blood, but a significant decrease in erythrocyte count occurred only in the high dose dimercaprol animals. Postmortem examination showed that all animals had hepatic cirrhosis, nephrosis, and splenic fibrosis. Cadmium concentrations of organs studied did not differ from group to group; they were 60, 30, and 24 mg/100 g wet tissue in liver, kidneys, and

spleens, respectively. It was concluded that dimercaprol had no prophylactic action on cadmium poisoning and probably enhanced the poisoning.

The evidence of renal damage with proteinuria in humans intoxicated by cadmium can be interpreted to indicate that protein metabolism is affected by cadmium. Lawford[144] observed two abnormalities in the protein pattern (a decrease in one component and a concomitant increase in two other components) in the serum of rats given 50 ppm Cd(II) as cadmium chloride in their drinking water for four weeks. Positive identification of one component band was not made. However, it was possible to bind radioactive iron to the increased components, which suggested that these bands were serum transferrin. In a study by Jacobs et al,[145] Japanese quail were fed a protein diet which contained 75 mg/kg of zinc and to which 75 mg/kg of cadmium chloride was added. Controls received the usual diet containing 75 mg/kg of zinc, since young quail are sensitive to zinc deficiency. After 4 weeks, 80% of the cadmium-fed birds developed severe anemia associated with an increased concentration of transferrin (15% in controls vs 23% in the cadmium group) and moderate decreases in the serum albumin (31% vs 27%) and lipoprotein fractions of the plasma. This resulted in a significant increase in the transferrin-albumin ratio (controls 0.49 vs cadmium group 0.86). The plasma protein electrophoretic pattern of cadmium-treated birds did not show the abnormal serum pattern described by Lawford[144]. The authors postulated that the effect of cadmium in elevating transferrin might be explained by the iron-deficiency anemia. Since transferrin functions as the iron donor and it is bound in this process, a lack of iron would allow the transferrin to be released into the blood and thus result in hypertransferremia. In a prolonged exposure study by Axelsson and Piscator[123], rabbits (Belgian Giant) were given daily sc injections of 0.25 mg/kg Cd(II) five days/week for 11-29 weeks. There was an initial reduction in serum albumin and an increase in α- and β-globulins. This appeared to be an acute reaction since prolonged treatment resulted in a decrease of the α_2-globulins. Haptoglobin determinations showed the development of ahaptoglobinemia after 11 weeks, indicating hemolytic anemia.

(c) Vascular Effects

Schroeder[88] attempted to duplicate the human condition of chronic hypertensive disease in small laboratory animals. Rats and mice were given trace amounts of cadmium (5 μg/ml) in their drinking water from the time of weaning. Cadmium produced hypertension in rats after approximately one year and this effect increased with age. The incidence in females was higher than in males. However, the mortality was greater in males with hypertension, and median life spans of both sexes were shortened compared to controls (156 vs 140 days, p less than 0.005). Schroeder[88] also reported results of another experiment in which 80% of rats receiving soft water were hypertensive by 500 days of age vs 17.7% of those rats receiving hard (calcium-containing) water. Another part of the study demonstrated that following the ip injection of cadmium acetate (1.5, 2 or 3 mg/kg) mean blood pressures (apparently systolic) were increased an average of 47 mm Hg. When cadmium-hypertensive rats were given a zinc chelate (2-diaminocyclohexane disodium zinc tetraacetate), they became normotensive within a week. Analyses for cadmium and zinc in the kidneys and liver of 90 hypertensive and normotensive rats suggested a reasonable correlation between the renal ratio of Cd/Zn with the level of blood pressure; hepatic ratios were not significant. A renal Cd/Zn ratio of more than 0.80 indicated hypertension. The author[88] suggested on the basis of his animal data that cadmium might be a factor in hypertension of unknown origin in humans.

Others[146-151] have also found hypertensive effects of Cd(II) in animals.

Porter et al[152] found no elevation of blood pressure in Cd(II) intoxication. They administered cadmium acetate ip at 2 mg Cd/kg to female Sprague-Dawley-derived rats, then a second ip dose of 1 mg Cd/kg 3 weeks later. From days 14 to 27 after the second administration, various autonomic drugs were administered in sequence by vein, and systolic blood pressures were recorded. With norepinephrine but not epinephrine, drugs causing elevated blood pressure in control rats, there was a lesser elevation in cadmium-treated rats; with acetylcholine, isoproterenol, and atropine, but not propranolol, drugs causing decreased blood pressure in control rats, there was a lesser decrease in cadmium-treated rats. Aortic strips from cadmium-treated rats had a diminished reactivity to angiotensin, epinephrine, barium, and tyramine. The authors concluded that cadmium desensitizes rat vasculature to vasoconstrictors and dilators independently of any ability to cause hypertension.

Fowler and coworkers[153] gave drinking water containing 0, 0.2, 2, 20, and 200 ppm Cd(II) as cadmium chloride to male rats for 6 or 12 weeks. Rats were also given a diet with normal (0.7%) or low (0.1%) calcium. The animals' feed also incidentally contained 0.4 ppm cadmium, so even controls were ingesting some Cd(II). (Similarly, animals in other experiments probably also ingested small amounts of cadmium normally present in feed.) Kidneys of animals on a low calcium diet had a higher cadmium concentration than those on a normal diet. The cadmium feeding caused constriction of smaller and dilation of larger renal arteries and a fibrosis of peritubular capillaries. There was an increased BUN but little tubule cell damage. The authors suggested that cadmium-induced vascular damage has a role in cadmium nephropathy. While dietary calcium did not influence the vascular effects of cadmium, the authors briefly referred to their unpublished observations that dietary calcium did affect blood chemistry and parathyroid glands in the same animals.

Singhal et al[154] have suggested that hyperglycemia and arterial hypertension from Cd(II) intoxication might be related to increased synthesis of epinephrine in adrenal glands. They injected cadmium chloride, 1 mg/kg ip, in rats daily for 45 days. Adrenal weights were increased, as were levels of adrenal norepinephrine and epinephrine and activity of adrenal tyrosine hydroxylase. Tyrosine hydroxylase activity and norepinephrine and epinephrine levels had returned to normal 28 days after the last Cd(II) injection, but the adrenals had only partially recovered their original weights.

(d) Reproductive Effects

Little attention had been drawn to the effects of cadmium on gonads prior to the mid-1950's when Parizek[91] and Parizek and Zahor[92] described the necrotic effects on testicular tissue in rats, which has since been confirmed by many others in several animal species. Parizek and Zahor[92] injected 80 male rats sc with 1 ml of 0.03 M solution of cadmium chloride. The rats were killed at various intervals from 2 to 48 hours after the injection. Microscopic changes in the testes were observed as early as 2-4 hours after injection, as evidenced by edema and capillary stasis. Testicular tissue damage progressively increased with time. After 48 hours, complete testicular necrosis was found in all 80 animals. Similar data were developed by Mason et al[155] at various doses of cadmium chloride (0.57-6.8 mg Cd/kg) given sc to rats. Again, edema preceded an ischemic necrosis which was associated with increased intratesticular pressure, hemorrhaging, and ultimate interference with testicular blood supply. In this study, a dose-response relation was found at the lower dose levels, 0.57-1.4 mg/kg. At the lowest dose, no effect was observed, at 0.85 mg/kg ischemic necrosis of seminiferous tubules occurred in 32% of the rats, at 1.1 mg/kg there was a 90% incidence, and at 1.4 mg/kg 100% of the rats had these injuries. It was suggested that the unusual sensitivity of the testes to cadmium was related to the unique vasculature, ie, pulseless, semistagnant flow, which might have facilitated alteration of capillary endothelial permeability by cadmium.

Sangalang and O'Halloran[156] studied testicular injury and changes in androgen synthesis in brook trout exposed to Cd(II) for 24 hours at 1, 2, or 25 ppm. Testes of the fish treated at 25 ppm showed extensive hemorrhagic damage. Formation of 11-ketotestosterone, 11-β-hydroxytestosterone, and testosterone from ^{14}C-pregnenolone in vitro was used to study the effects of Cd(II) exposure on androgen synthesis by the testes. The results showed that cadmium inhibited the formation of the steroids in vitro; whether this reflects the situation in vivo is not known. However, the study suggests that cadmium-induced testicular damage is not confined to species with scrotal testes.

In order to investigate the testicular damage from cadmium in more detail, Parizek[91] injected rats and mice with cadmium chloride (2.2-4.5 mg Cd/kg) into the interscapular region sc. Some of the rats were treated with testosterone (1 mg/ml in olive oil) or zinc acetate (0.2 moles). Microscopic changes (hyperemia and interstitial edema) in the testes of cadmium-treated animals occurred within a few hours after injection. Forty-eight hours later, there was destruction of tubular epithelium, and interstitial tissue was hemorrhagic. After 10 days, there was replacement of testicular tissue by eosinophilic material. There was also a decrease in weight of the accessory sex organs, seminal vesicles, and prostate glands. However, when testosterone was given 10 days after the cadmium, the weights of these glands increased again, suggesting that the weight loss was the consequence of a hormone deficiency. Doses of zinc acetate 80,

100, and 200 times that of Cd(II) (3.33-4.8 mmole zinc acetate/kg) administered before, during, and after the Cd(II) prevented the testicular damage. The protective effect of Zn(II) against cadmium-induced testicular damage was confirmed by Webb,[157] who suggested that prior injection of zinc induced hepatic synthesis of a specific binding protein that immobilized cadmium. Protective effects by Zn(II) or Se(IV) against injury by Cd(II) to rat testes were also found by Kar et al[158] and by Mason and coworkers.[159,160]

Since the injury to rats' testes does not occur before the age of 7-16 days, the possibility that a hormonal balance in immature animals prevents testicular vascular damage from cadmium was investigated by Gunn et al.[161] Four groups of mature male mice were injected sc with 0.03 mmole/kg cadmium chloride (3.4 mg Cd/kg). Each group received 0.1 ml of either saline solution, sesame oil, testosterone (100 μg), or estradiol (100 μg) 3 times/week for 7 weeks. The cadmium treatment consistently produced vascular damage to the testes, characterized by marked edema, capillary hemorrhage, and tubular necrosis. Treatment with testosterone did not alter this response; however, estradiol protected the testes from vascular damage. This protective action of estradiol was reversible, since the testes were again susceptible to vascular damage by Cd(II) when the estradiol treatment was stopped.

Nordberg[162] gave CBA mice single sc injections of cadmium chloride at 1 mg Cd/kg, causing complete testicular necrosis. Single doses of 0.25-0.5 mg/kg caused little or no testicular damage. When these lower doses were administered 5 days/week for 6 months, testicular changes were slight at 0.5 mg/kg and within control limits at 0.25 mg/kg, though testicular cadmium levels were 6-7 ppm, compared with 0.3 ppm after single injection at 1 mg/kg. Repeated administration of 0.25 mg/kg, to induce metallothionein synthesis, protected the mouse testes from the necrotizing effect of a subsequent injection of cadmium chloride at 1 mg Cd/kg. When cadmium partially bound to metallothionein was injected at 1.1 mg/kg, no testicular necrosis developed. When CBA mice were given sc injections at 0.25-0.5 mg/kg 5 days/week for about 6 months[163] kidney damage occurred, as evidenced by proteinuria, altered composition of urine protein on electrophoretic examination, and a marked increase in urine cadmium concentrations at the time of development of electrophoretic patterns of urine protein judged to be pathologic. Similarly, rabbits administered cadmium chloride sc 5 days/week for 24 weeks at 0.5 mg Cd/kg did not develop macroscopically or microscopically evident testicular changes, though marked kidney damage developed.[164] This suggests that repeated administration of cadmium compounds at doses that cause slight or no kidney malfunction will not cause testicular damage.

Madlafousek et al[165] found that the copulatory activity of most male rats tested was lost within 3 weeks of injection with cadmium chloride at a dose previously found in that laboratory[91] to cause complete testicular necrosis and permanent sterility. The effect could be prevented by administration of androgens. Two months after Cd(II) administration, there was only slight impairment of sexual behavior; normal copulatory activity and ejaculatory behavior accompanied by the production of plugs had resumed in these animals. Spontaneous restitution of normal sexual activity did not occur in surgically castrated males.

Friberg et al[1] (pp 124-27) have reviewed results from investigations of testicular necrosis from Cd(II) and have persuasively argued that damage to the germinal epithelium is probably secondary to cadmium-induced vascular damage.

Studies of the marked effect of cadmium on male gonads stimulated several studies of possible effects on ovaries. Experiments have shown that sc injection of Cd(II) has a sterilizing effect on the ovaries of rats and gerbils.[166-169] Kar et al[166] reported acute changes in ovaries of prepubertal rats (6-8 weeks old) following administration of cadmium chloride sc at 10 mg/kg. Cadmium treatment had an insignificant effect on ovarian and uterine weights, but the rate of follicular atresia was markedly changed. Initially, the large- and medium-sized follicles were damaged; granulosa cells and ova showed signs of atrophy. At 48 hours after injection, all follicles were destroyed. Response of the ovaries to exogenous gonadotropin was inhibited. The authors suggested that the observed atresia might be due to interference with pituitary factors. Parizek et al[167] injected 5-day old female rats with either testosterone or 19-nortestosterone. After 3-6 months, the rats had a persistent estrus, after which they were injected sc with cadmium chloride or acetate at 0.02-0.04 mmole/kg. All ovaries examined had massive hemorrhages ac-

companied by necrosis. Kaul and Ramaswami[168] compared the effect of a single sc injection of Cd(II) on the ovaries of either mature or immature female gerbils. Mature animals were given 0.45 and immature animals 0.22 mg/kg. There were no significant changes in ovarian weights of immature gerbils, but there was a gradual reduction in ovarian weights of adult females. There were extensive hemorrhages and widespread atresia in both mature and immature female gerbils.

Whether the follicular atresia is from a direct effect of cadmium on germ cells or a secondary effect from alterations in blood, especially capillary, supply, is not known. The latter effect was suggested by the development of placental necrosis in pregnant rats.[169]

Kar et al[158] found that simultaneous injection of zinc acetate or selenium(IV) oxide and cadmium chloride into rats did not result in the ovarian damage produced by cadmium chloride alone.

Tsvetkova[95] exposed groups of female rats to cadmium sulfate for up to 7 months at 2.8 mg/cu m. At 2 months 50% and at 4 months 75% of the animals had a prolongation of the estrous cycle. Litter sizes were the same in exposed and control rats, but neonates from exposed dams were smaller and weighed less than those from controls. Fetuses taken from exposed dams on the 22nd day of pregnancy had a higher cadmium level in the liver than fetuses taken from control rats.

Parizek et al[170] found that injection of cadmium acetate in the range of 30-40 μmole/kg in several groups of pregnant rats caused 40% of the pregnant rats to die within the first 24 hours after cadmium administration. The rats were injected on the 21st day of pregnancy. In 80% of these pregnant rats, bilateral hemorrhagic renal necrosis was observed.

Chernoff[171] administered 4-12 mg/kg cadmium chloride to CD-strain rats sc on 4 consecutive days beginning on day 13, 14, 15, or 16 of gestation. There was a dose-related increase in fetal deaths, decrease in fetal weight, and increase in rate of anomalies, which included micrognathia, cleft palate, clubfoot, and small lungs. He concluded that the decrease in lung size, observed in fetuses from animals injected at 8 mg/kg on days 14-17 of gestation, was a specific retardation rather than the result of overall growth retardation. He did not find a basis for concluding whether the fetal anomalies were the result of a direct action on the fetus, placental effects, maternal effects, or a combination of these factors. Data on deaths of dams were not reported, from which it is inferred that none occurred.

Barr[172] found that cadmium chloride (16 μmole Cd/kg) was not teratogenic when administered sc to 2 different stocks of Wistar rats on day 9, 10, or 11 of gestation, but was when administered ip. There was uniformly a weight loss in dams after ip Cd(II) for 1 or 2 days, but in 2-4 days more their weights returned to preinjection values or more; by 21 days, injected rats did not differ significantly in weight from control rats. Rats given Cd(II) sc had little or no weight loss. Doses greater than 22 μmole Cd/kg often killed pregnant rats. Anophthalmia or microphthalmia was found in the greatest number from Cd(II) administration on day 9 and was seldom found when cadmium was given after day 9. Dysplastic or absent ears were found only after administration of cadmium on day 9. Few facial malformations were seen, in contrast to the findings of Mulvihill et al[173] in hamsters. Hydrocephaly was often observed after administration of cadmium on day 9 or 11, but not when cadmium was given on day 10. There were a few cases of encephalocele and exencephaly in day-9 and day-11 groups. A thin abdominal wall (less than 0.5 mm) was seen, especially in day-9 rats, and correlated highly with a left-sided umbilical artery, ear dysplasia, undescended testes, and renal agenesis in one stock of Wistar rats but not in the other stock. Other changes seen in some groups of at least one strain were diaphragm hernia, anal atresia without gross abnormalities of the gut, dysplastic or absent tail, hydronephrosis, and a small rate of appearance of dysplastic forelimbs. The authors suggested that cadmium-induced interference with zinc metabolism might explain some of the changes seen, at least the limb defects.

Ishizu et al[174] administered cadmium chloride sc to pregnant mice on the 7th day of gestation at doses of 0.33-5 mg/kg. An increased rate of malformations was not seen at 0.33 mg/kg, but there was a dose-related increase at higher doses (0.63, 2.5, and 5). Exencephaly was the most common change in these fetuses, taken from the dams on the 18th day of gestation, and many of the exencephalic animals had their eyes open. There were also spina bifida, absence of tail, and vaginal atresia. There were malformations in the ribs as well as in the skull and vertebrae. Some dams in all

cadmium-injected groups aborted; in addition, dams did not have weight increases expected during pregnancy. Amniotic fluids observed during removal of fetuses were hemorrhagic. Total fetal cadmium concentrations were not significantly increased, but placental concentrations were.

Investigators in Ferm's laboratory[173,175,176] performed several studies, all involving injection of cadmium sulfate by vein into pregnant hamsters, at a dose of 0.88 mg Cd/kg. Gale and Ferm[175] administered the cadmium sulfate on the 8th or 9th day of gestation, and fetuses were removed from dams on the 15th day. The most frequently observed malformations were in the brain (exencephaly and encephalocele), eye (anophthalmia, microphthalmia, and exophthalmos), jaw (cleft lip and micrognathia), tail, and forelimbs and hindlimbs (amelia, micromelia, and ectrodactyly). Malformations of the head were seen more frequently in animals injected on the morning of the 8th day, while the limbs were more likely to be malformed in animals given cadmium on the evening of the 8th day or the morning of the 9th day. The authors suggested that some of the malformations might be the result of an effect of Cd(II) on the permeability of the mesenchymal cell membranes. Ferm[176] also administered the cadmium salt on the 8th or 9th day of gestation, and again the dams were killed on the 15th day and fetuses removed for examination. Facial malformations and exencephaly were more frequently found in fetuses from animals given cadmium on the morning of the 8th day than in those from animals injected on the evening of that day, while injections at the latter time caused more rib and forelimb malformations. Fetuses from animals injected on the 9th day had mostly rib and limb defects. Mulvihill et al[173] injected the cadmium salt on the 8th day of gestation and removed the fetuses on the 12th, 13th, or 14th day. Heads of fetuses were fixed and processed for palatal examination. Cadmium-induced changes in facial development included unilateral and bilateral cleft lips and palates, in addition to abnormalities in cartilage formation and delayed ossification. The authors suggested that these effects were the result of mesodermal deficiency rather than of a delay in transposition of the palatine shelves, but could not determine whether this was from a specific action on maternal metabolism with secondary effects on differentiating embryonic tissues or an interference with placental transfer of an essential metabolite. They did not comment on whether a cadmium-induced zinc deficiency might be the proximal cause of either of these mechanisms.

In other studies of the teratogenic effects of cadmium, Ferm and Carpenter[177,178] showed that Zn(II) inhibited the teratogenic effect of Cd(II). Administration of cadmium sulfate to hamsters by vein at 0.88 mg Cd/kg caused abnormalities similar to those seen in other studies (cleft lips and palates, microphthalmia and anophthalmia, and encephalocele and exencephaly).[177] Simultaneous administration of zinc sulfate at 0.45 mg Zn/kg reduced embryonic resorption and malformation rate to control levels. If the injection of Zn(II) was gradually delayed after Cd(II) injection, the protective effect lessened, and no protective effect was evident after a delay of 12 hours or more. Cobaltous acetate did not have a similar protective effect on Cd(II)-induced terata. Pathologic changes were not seen in dams injected with both Zn(II) and Cd(II).[178]

These studies of teratogenicity usually analyzed data by considering the individual fetus as the treatment unit. While the litter rather than the individual animal or fetus might be better as the unit for comparison, it is doubtful that different conclusions on cadmium teratogenicity would have been reached thereby.

Wills et al[179] studied the effects of Cd(II) on reproduction and on blood pressure in rats and monkeys. Male and female rats were given feed containing cadmium chloride at 33 or 73 ppb. Monogamous matings were performed and continued until 4 litters/couple had been delivered. Offspring and subsequent generations were similarly fed and paired except for a few from the first and fourth litters and all animals from the second and third litters of each generation. These animals and animals dying during the experiment or killed at its end were examined macroscopically, and, in the case of abnormal tissues and organs, microscopically. Reproduction was continued for a total of 4 generations. The lower concentration (33 ppb) had little effect. At the higher dose level (73 ppb), there was a slight increase in fertility, especially in the last two litters in each generation. There was a slight increase in longevity of animals fed at 33 ppb and a slight decrease at 73 ppb. There was a deficit in weight gain, greater at 73 than at 33 ppb. There were initial increases

in systolic blood pressures, but these were within the range of control values, and they later subsided, suggesting to the authors that Cd(II) increased neurogenic hypertensive activity which disappeared as the rats became accustomed to the pressure-measuring procedure.

There were no significant macroscopic or microscopic changes in the 276 rats examined. Changes seen were usually of a minor nature and were attributed to spontaneous disease. Tumors were of various types and not significantly different in controls and test animals. A noteworthy finding was the absence of kidney or important vascular lesions. In fact, the authors[179] concluded that feeding of Cd(II) at the lower of these two doses may have been beneficial.

They also fed four female monkeys cadmium chloride in a sweetened beverage at 1.5 and 3.0 μg/kg/day, with 2 monkeys at each dose level and a fifth as a control. The control monkey and one at 1.5 μg/kg/day died after about 6 months, apparently from disease unrelated to Cd(II) ingestion. The three remaining animals survived the 18 months of treatment. They were mated with normal males, following which two, one at each dose level, became pregnant. Both delivered one infant, the one at the lower dose prematurely. Both infants nursed and developed normally, and neither appeared to have any abnormalities. Systolic blood pressures of the dams were not significantly affected by Cd(II) ingestion; however, the number of animals was too small for statistical validation.

Epstein et al[180] studied 174 compounds, including cadmium chloride, for their ability to cause mutations in mice by a modified dominant lethal assay. Cadmium chloride was administered to male mice ip at 1.35-7.0 mg/kg. Detailed data on those substances not causing significant evidence of mutagenic activity, including cadmium chloride, were not presented; however, according to a footnote, early fetal deaths and preimplantation losses from cadmium chloride were within control limits, but there was a reduced rate of pregnancy. This suggests that Cd(II) may have caused testicular dysfunction in the treated males prior to mating, which might have made the dominant lethal assay less sensitive for this compound. Gilliavod and Leonard[181] also found no increase in dominant lethal mutations from administration of cadmium chloride to male BALB/c mice. They injected cadmium chloride ip at 0.5, 1.75, or 3.0 mg/kg and injected controls with saline solution. Mice administered 1.75 mg/kg were mated, after which pregnant females were examined for corpora lutea, implantations, and live and dead embryos. Pregnancy rates were 45-68% in test animals and 57-68% in controls. There was no increased incidence of dominant lethal mutations in test animals over that in controls. All sires were killed 3 months later and dividing spermatocytes were found not to have chromosomal rearrangements such as reciprocal translocations. Similarly, male offspring of mice injected at 1.75 mg/kg were found not to have translocations.

NIOSH has indicated its interest in possible teratogenic or mutagenic effects of some chemical agents, including cadmium, in the *Federal Register* 41:12731-32, March 26, 1976. This statement of concern was based on unevaluated information in the 1976 edition, being prepared for publication, of NIOSH's *Registry of Toxic Effects of Chemical Substances*, which refers to several reports of experimental teratogenicity[171,172,178] and to a separately published abstract of one of these reports.[171] These studies, together with additional investigations of experimental teratogenicity, have been reviewed in the discussion above.

(e) Carcinogenesis

In 1967, Gunn and associates[182] reported that 4 sc doses of 0.17 mg of cadmium chloride produced pleomorphic sarcomas at the site of injection 12-16 months later in 3 out of 30 male Wistar rats. Others[183-187] have also induced injection-site sarcomas in rats by suspensions of CdO, CdS, $CdSO_4$, or Cd metal powder. Injection of cadmium chloride sc at 30 μmole/kg also caused, in addition to injection-site sarcomas, interstitial cell tumors of testes.[188,189] However, injection of zinc acetate (3 mmole/kg) inhibited the development of both types of tumors resulting from Cd(II) injection.[188,189] Cadmium sulfate or cadmium-precipitated ferritin injected sc or po in rats and mice also caused testicular atrophy, often followed by hyperplasia of Leydig cells which in rats tended to progress to neoplasia.[190]

In a series of experiments reported by Schroeder and coworkers[191] and by Kanisawa and Schroeder,[192] Long Evans rats were given water containing cadmium acetate at 5 ppm from weaning to death (up to 4 years). In some experiments, other metals were included in the drinking water.

Longevity of male rats fed Cd(II) exceeded that of controls, but that of female rats was less than controls. Cd(II)-fed rats did not have a significant increase in tumors above the incidence in controls.

Levy and coworkers[105-107] investigated in rodents the ability of Cd (II) to cause prostate cancer. They injected cadmium sulfate sc once a week into the flanks of specific pathogen free (SPF) CB-strain hooded rats for two years at dose levels of 87, 44, 22, or 0 μg Cd/kg,[105] and 3 times/week introduced cadmium sulfate through an intragastric catheter into the stomachs of SPF CB rats for 2 years at 350, 180, 87, or 0 μg Cd/kg[106] and of Swiss mice once a week for 18 months at 1.75, 0.88, 0.44, or 0 mg Cd/kg.[107] Rats injected sc at 87 mg/kg had a significant decrease in weight gain but not rats injected at lower doses. No other changes in experimental animals attributable to cadmium were found except for a low incidence of injection-site sarcomas and for cadmium accumulations in spleens, livers, kidneys, and testes in sc-injected rats, with the most marked accumulations in the kidneys. There was no evidence of an elevated incidence of proteinuria in rats, above that high incidence common to older rats of the CB strain. There was a high incidence of testicular changes and Leydig-cell tumors common to both treated and control rats. There were no prostate neoplasms or pre-neoplastic changes in the prostate glands of either rodent species. However, the near absence of toxic changes from Cd(II) in these experiments raises a question whether the doses administered were high enough to produce prostate neoplasms, assuming such a capability by cadmium.

In a screening study[193] of possible carcinogenicity by a large number of compounds, ethyl cadmate (cadmium diethyl dithiocarbamate) caused an increased incidence of tumors in mice treated sc or po. However, several other dithiocarbamates also caused an increased incidence of tumors in mice in this study, so it is likely that this tumorigenesis resulted from the dithiocarbamate rather than from the cadmium.

NIOSH stated its concern about possible tumorigenicity of a number of chemicals including cadmium in an announcement in the *Federal Register* 40:26390-496, June 23, 1975. This concern was based on then-unevaluated reports of neoplastic effects listed in the *Registry of Toxic Effects of Chemical Substances*. In the 1976 edition of this NIOSH registry being prepared for publication, there are several references on possible tumorigenicity of cadmium compounds which have been cited in the discussion above. [182-185,187-189,193] One additional reference in the registry not discussed above is to the IARC review of cadmium.[4] This review summarized results of several experimental and epidemiologic studies giving information relevant to carcinogenicity of cadmium compounds, and suggested that the data were insufficient to permit conclusions on whether or not cadmium is carcinogenic.

(f) Biochemical Studies

A significant factor in the absorption, distribution, and retention of low and moderate levels of oral or parenteral Cd(II) is the presence and possibly the induced synthesis of the low-molecular weight protein thionein, which binds certain heavy metals to form metallothioneins.

Metallothionein was first isolated by Margoshes and Vallee[194] from horse kidney cortex and was shown to contain a high concentration of cadmium with a lesser amount of zinc. Subsequently, Kagi and Vallee[195,196] purified this material, showing that it was a homogeneous, low molecular weight protein (10,000 mol wt) containing 5.9% cadmium, 2.2% zinc, and 8.5% sulfur, and having very low spectral absorptivity at 280 nm, indicating a lack of aromatic amino acids in its composition but with a specific absorptivity at 250 nm due to cadmium-sulfur groupings. These investigators suggested that the metal-free protein be called thionein, and that the cadmium protein be called cadmium-thionein. Ninety-five percent of all sulfur in the metal-free thionein molecule was present as the sulfhydryl group of cysteine. Moreover, cysteine accounted for 1 of every 3 to 4 amino acids, ie, 25-30% of the amino acids of this protein are cysteine molecules. Pulido et al [197] showed that a similar protein could be isolated from human renal cortex. This purified metallothionein had a molecular weight of 10,500 and contained 4.2% cadmium, 2.6% zinc, 0.5% mercury, and 0.3% copper. As with the equine protein, the sulfur content was high, namely 8.1%, and the characteristic ultraviolet absorption band at 250 nm was present.

Following these early reports from the Harvard group,[194-197] one group of workers at the Karolinska Institute in Sweden[198] and another at Dalhousie University in Nova Scotia[199-201] have found that there are two cadmium-binding proteins, both

of which are of low molecular weight (10,000-12,000) with high sulfur content, in rabbit and rat liver. Two forms of cadmium-thionein found by Nordberg and coworkers[198] differed slightly in amino acid content other than cysteine and had isoelectric points (pI) of 3.9 and 4.5. The protein with pI 4.5 contained zinc as well as a lower amount of proline and a higher amount of glutamate than did the form with pI 3.9. The molecular weights of both the fractions were estimated to be about 6,000; possibly, but not likely, the molecular weights were an integral multiple of 6,000. There is no evidence of the existence of isomorphic forms of thionein, but it seems possible that thionein represents a family of low molecular weight proteins containing large amounts of sulfur and which bind heavy metals in general.

The capacity of thionein to bind heavy metals suggests a possible role in heavy metal metabolism or as a detoxifying mechanism. Thionein in its various metal forms has now been found in liver, kidney, testis, spleen, pancreas, and intestines of mice, rats, monkeys, and man, indicating by its wide distribution a probable role in cadmium metabolism and toxicology.[194-198] This is best illustrated at present by the induction of thionein biosynthesis by administration of low initial levels of Cd(II).[202,203]

In his studies, Webb[204] showed that thionein is induced by Zn(II), Cd(II), and Hg(II), but not by Cu(II), Ni(II), or Pb(II). Its synthesis was inhibited by cycloheximide but not by actinomycin D, which suggests that induction of thionein is controlled at the translational level and not at the transcriptional one. From these and other facts, Webb suggested that thionein is a part of a mechanism that has a relatively specific affinity for Group IIB elements and not for heavy metals in general.

Grasso,[205] in a review of morphologic and biochemical studies of the effect of cadmium on renal function, has suggested that any protection against renal damage afforded by thionein is probably limited, in view of the rather small amounts of cadmium that can cause morphologic and functional changes in the kidney. Nordberg et al[206] found that cadmium-thionein caused a greater degree of damage to renal tubules and was lethal at lower doses than cadmium chloride in CBA mice administered these forms of Cd(II) iv or sc. As was reviewed earlier, metallothionein can protect mouse testes from cadmium-induced injury.[162,164]

Phosphorylation coupled to aerobic oxidation of succinate or reduced diphosphopyridine nucleotide is uncoupled at low concentrations of Cd(II).[207,208] In rat liver mitochondria, [207,208] addition of Cd(II) in vitro uncoupled phosphorylation, at a low concentration (5 μM). This was observed with the oxidation of both succinate and citrate. The uncoupling effect of cadmium was completely reversed by the chelating agent ethylene diamine tetraacetic acid. In a more recent study by Mustafa and Cross[209] using pulmonary alveolar macrophages, the inhibition of oxidation by Cd(II) in the cells and mitochondria of this preparation was demonstrated. Both phosphorylation and respiration were abolished with 5-10 μM Cd(II). The uncoupling action appears to involve the binding of cadmium to dithiol groups of the enzymes. Many heavy metals combine with -SH groups and a large number of enzymes contain -SH groups which are required for their activity. If heavy metals combine with these -SH groups, the enzymes would likely be inhibited. Using succinoxidase, a sulfhydryl enzyme, Barron and Kalnitsky[210] studied the effects of a number of heavy metals on this enzyme-metal complex. Cadmium, bismuth, and mercury had the greatest inhibitory effects, producing 50% inhibition at concentrations of 7,12, and 12.5 μM, respectively. Webb[204] found that in addition to the inhibition of α-oxoglutarate dehydrogenase by heavy metals at the -SH groups, other metal-sensitive sites were involved. These sites were sensitive to inhibition by cadmium, zinc and copper.

Glucose is metabolized by a number of phosphorylating enzymes to yield high energy phosphate compounds. The effect of Cd(II) on glucose metabolism has been studied both in vivo and in vitro. Harkonen and Kormano[211] injected rats with Cd(II) and determined the major energy metabolites in the testes. Following the sc injection of 0.04 mmole/kg of Cd(II), rats were killed at 0.5, 1,2 and 4 hours and the testes removed. Glucose concentrations increased significantly at 30 minutes and again at 2 hours. There was a marked decrease in glucose-6-phosphate and adenosine triphosphate at 2 hours. Glycogen and total high energy phosphate were considerably lowered at 4 hours, at which time lactate concentration was increased. It was suggested that the decrease in high energy metabolites might be related to the ischemic or anoxic state of the rat testes. In a

recent report from Canada,[212] the effect of cadmium on the glucose synthesizing enzymes (gluconeogenesis) in the liver and kidney was studied in vivo. Rats received daily ip injections of cadmium chloride (1 mg/kg) for 45 days; controls were given saline. To determine the effect of cadmium withdrawal, other rats which had received the same treatment were maintained without further cadmium administration for another 28 days. Cadmium enhanced gluconeogenesis, as was evidenced by increased activities of four glucose-synthesizing enzymes in both the liver and kidney. This was correlated with an increase in blood glucose levels and a concomitant decrease in liver glycogen. Discontinuation of the daily injections of cadmium for 28 days failed to reverse the increases in glucose synthesis found in the liver and renal cortex. The data suggested a possible biochemical basis for some of the toxic effects exerted by cadmium. These observations were in direct contrast with an earlier study of Rutman et al [213] on the effect of metal ions in vitro on gluconeogenesis by rat kidney cortex. Of a number of metal ions whose effects on glucose formation were examined, Cd(II) exerted the greatest inhibition.

Cyclic adenosine monophosphate (AMP) metabolism was examined to determine whether the testicular damage following exposure to cadmium was related to changes in this mediator.[214] Rats were injected ip with 1 mg/kg cadmium chloride daily for 45 days. Testicular and prostatic as well as body weights were decreased in the cadmium-treated rats compared to controls. Cyclic AMP levels in testes were unchanged because, though adenyl cyclase was significantly increased, the increase was offset by a concomitant increase in phosphodiesterase activity. Cyclic AMP-dependent and AMP-independent forms of testicular protein kinase were decreased in activity, but the binding of cyclic AMP to protein kinase was not affected. The results were opposite in the prostate gland, ie, there was a decrease in cyclic AMP, attributed to a decrease in activity of adenyl cyclase; cyclic AMP binding to prostatic protein kinase was increased, together with an increased activity of cyclic AMP-dependent protein kinase.

Kench and Gubb[142] found cadmium intoxication in the chick to result in inhibition of lipoamide dehydrogenase, δ-aminolevulinate synthetase, and xanthine dehydrogenase. They also found an impairment in the in vivo biosynthesis of catalase, a heme-containing enzyme.

Ribas-Ozonas and coworkers[215] found Cd(II) to cause a significant decrease in the activity of alkaline phosphatase (a zinc-containing enzyme) in both kidney and prostate gland in guineas pigs. They did not find any effects on acid phosphatase and esterase activities. Vigliani[67] found a severe reduction in kidney leucineaminopeptidase activity in mice after Cd(II) administration at 50 μg/day for 5 days.

(g) Interaction with Zinc and Other Metals

The fact that cadmium is in the same group of the Periodic Table as zinc, ie, IIB, has led to research on the question of whether cadmium interferes with the metabolism of the essential element, zinc. Similarly, since cadmium occurs in solution in only one valence state—Cd(II)—and binds to -SH groups, as do other heavy metals including copper, there have been several investigations of whether the metabolism of any of the common essential divalent minerals could be affected by the presence of Cd(II).

Supplee,[216] in a study of poultry growth, and Cotzias et al,[217] in a study with rabbits, developed evidence of an antagonistic effect of zinc and cadmium, with a suggestion[218] that cadmium might in part act as an antimetabolite for zinc.

Hill et al[219] reported evidence that Cd(II) interfered with the metabolism of copper and iron, as well as zinc, in a study on chicks; additional amounts of these essential metals reversed some or all of the adverse effects of cadmium. Bunn and Matrone[220] showed similar interactions in rodents. Lease[221] reported evidence that Cd(II) given orally to chicks decreased the intestinal tract absorption of zinc and postulated that cadmium interferes with zinc absorption by occupying the same transport binding sites.

Parizek and colleagues[222] found that the lethality of injected cadmium chloride in rats could be greatly reduced if zinc chloride or zinc acetate were injected 5 hours prior to the cadmium dose. Cupric chloride did not have this protective effect. These results, together with those previously cited, suggest that zinc could alter the acute and chronic toxic action of orally or parenterally administered Cd(II) by competing for receptor sites of cadmium.

Petering and coworkers[223] showed that Cd(II) administered in the drinking water at a concentra-

tion of 3.4 μg/ml caused definite alteration of both zinc and copper metabolism when dietary zinc was suboptimal and the Zn/Cd ratio was 1, but that these effects could be prevented by raising the level of dietary zinc to a Zn/Cd ratio of 4/1. The increased amount of dietary zinc did not affect the elevated level of cadmium in blood or kidney, but it did inhibit the increase in the liver concentration of cadmium. Under these conditions of low intake of cadmium, there was no evidence of testicular effect or accumulation of cadmium in the testes. When the Zn/Cd ratio was 1, testicular zinc levels were significantly lower than normal, but at a 4/1 ratio, testicular zinc concentrations were normal. This suggests an indirect effect of cadmium on zinc metabolism in testes.

Webb,[157] using high doses of injected Cd(II), found that prior injection of Zn(II) in rats protected testes from the adverse effects of cadmium and caused the synthesis of the cadmium-binding protein thionein in the livers of rats.

Starcher[224] and Evans and coworkers[225] have reported that copper and zinc absorption in the gut involves a thionein-like protein, the sites of which are blocked by cadmium. Following the oral administration of ^{64}Cu (1-30 μg as the nitrate salt) to chickens,[224] absorption was greatest in the duodenum. The radioactive copper was bound to a protein of low molecular weight (10,000). Both zinc and cadmium antagonized the binding of copper to its protein complex.

As was discussed earlier in this Section, Zn(II) can also prevent various experimental effects of Cd(II), such as hypertension,[88] fetal abnormalities,[177,178] ovarian damage,[158] or testicular injury.[91,157-160,223] It also prevented the development of tumors at the site of sc Cd(II) injection as well as those remote from the injection-site, ie, in the testes.[188]

In addition to the protective action of dietary zinc and copper and of the induction of thionein synthesis in response to administration of cadmium, other physiologic and nutritional factors have been ascribed a protective role against cadmium toxicity. Gunn and coworkers[226] have shown that estrogens reduce the damage to the testicular vasculature of rats caused by cadmium chloride at sc doses of 3.36 mg/kg. Gunn and coworkers[161,227] have also reported that cysteine and other thiols protect against some of the testicular damage due to parenteral cadmium.

Selenium also can antagonize cadmium toxicity.[158-160,228] Simultaneous sc administration of cadmium chloride and sodium selenite resulted in the appearance of a peak blood concentration of cadmium about 13 times that caused by injection of the same amount of cadmium alone.[228] The decrease in toxicity of cadmium by the combined administration, as well as the elevated concentration of cadmium in the blood, was attributed to blockage by selenium of uptake of cadmium into tissues. This results, then, in both retention of cadmium within the blood and, presumably, its increased excretion from the body in correspondence with its markedly elevated concentration in the blood. Holmberg and Ferm[229] found that selenium as sodium selenite protected hamsters from the teratogenic effects of cadmium administered by vein to the dams. As discussed earlier, selenium can also prevent cadmium-induced ovarian[158] or testicular injury[158-160] in rats. The effect of selenium may be related to a chemical similarity to sulfur and to the ability of sulfur to complex or otherwise detoxify various metal salts.

(h) Other Effects

Several investigators have studied the possibility that hyperglycemia and glucosuria in cadmium intoxication might be due to pancreatic effects. Ithakissios et al[230] injected rats every other day for a total of 70 days with cadmium acetate solution at 0.25-0.50 mg Cd/kg ip. One group of rats had their pancreata perfused with buffered glucose solution, while other treated rats were studied for changes in plasma glucose, immunoreactive insulin (IRI), and urine glucose, following which $^{14}CO_2$ radiorespiration was studied. Pancreata from animals given 0.5 mg/kg secreted less insulin, but there were no significant changes in plasma glucose or insulinogenic index (ratio of plasma insulin to glucose). Treated animals excreted less radioactive carbon dioxide from the lungs than controls, and excreted more radioactive carbon and more glucose in the urine. IRI released during perfusion was decreased.

Ghafghazi and Mennear[231] came to a similar conclusion that cadmium affected pancreatic function based on their perfusion of isolated rat pancreata with 0.5-1 mM Cd(II) and finding inhibitions of the secretion of insulin in response to glucose, tolbutamide, and potassium.

Nomiyama et al[232] found evidence that aminoaciduria and enzymuria are earlier indices of

renal changes than proteinuria or glycosuria. They administered cadmium chloride to rabbits in the diet at 300 ppm Cd for up to 54 weeks. Aminoaciduria and enzymuria were detected after 14-16 weeks. Anemia was observed after 27 weeks; later, proteinuria and glycosuria appeared. There was loss of body weight and appetite after 42 weeks. There was no evidence of osteomalacia. They concluded that excretion of amino acids and enzymes in the urine can be used to detect early cadmium intoxication, whereas tests of tubular function should be useful to detect later cadmium nephropathy. However, their method for detecting urinary protein (a semiquantitative application of the biuret reaction) may not have been sufficiently sensitive to allow reliable estimation of small concentrations of urine protein. Axelsson and Piscator[233] found significant increases in amino acid excretion in the urine of cadmium-intoxicated rabbits only after development of proteinuria, as detected by more sensitive methods for protein determination. They administered cadmium chloride sc at 250 μg/kg to groups of Belgian Giant rabbits 5 days/week for 11, 17, 23, or 29 weeks; another group was similarly administered cadmium chloride for 24 weeks and observed an additional 25 weeks. Renal tubular changes were judged from microscopic examination of tissues, by a glucose reabsorption test, by alkaline phosphatase activity changes in the renal cortex, and from electrophoretic examination of urine protein; glomerular filtration was judged from a creatinine clearance test with extrinsic creatinine. Renal tubular damage was localized to the proximal segment. In rabbits exposed for a longer period, there were some microscopic changes in the glomeruli without definite impairment of the filtration rate. Cadmium was deposited mainly in the renal cortex, largely in the proximal segment of the tubules but also, to a lesser degree, in the distal tubules but not in the collecting tubules, glomeruli, or stroma. Excretion of cadmium in the urine increased greatly after renal damage occurred, correlating with proximal tubule function; eventually, after renal damage had occurred, cadmium was excreted in the urine in greater daily amounts than were being administered daily. Most of the cadmium in the urine was bound to colloids or cells.

In cats, fatty infiltration of the liver has been described[80] following exposure at high concentrations of cadmium oxide fume or dust, but not cadmium sulfide, for short periods of time. Liver enzyme changes were noted in animals given 1 ppm Cd(II) in drinking water (as cadmium chloride) for 11 months.[234] There was evidence of alterations in hepatic carbohydrate metabolism, ie, there was an increase in phosphatase and a decrease in aldolase activity. When larger amounts (10 ppm) were given for short periods, 60 days, oxidative phosphorylation activity in hepatic mitochondria was altered, ie, there was an uncoupling action by Cd(II). Cd(II) did not affect mitochondrial oxidative phosphorylation when fed at 1 ppm in water for a long period, 335 days.

The possible relationship of cadmium administration to dental caries has been investigated. Ginn and Volker[235] administered 50 ppm Cd(II) (as cadmium chloride) in food or in water to rats for 150 days; other rats were administered fluoride. Unlike fluoride, cadmium did not inhibit development of caries, and it may have increased caries susceptibility. Cd(II) decreased the degree of pigmentation of incisor enamel in these rats, and there was a reduction in blood hemoglobin. The authors suggested that the effects on enamel and blood were the results of interaction of cadmium with iron-containing proteins. In another experiment with rats given 40 ppm cadmium chloride in drinking water during the period of calcification of molars,[236] there was no increase in numbers of carious lesions, but there was an increase in their rate of progression, attributed to Cd(II) intake.

Correlation of Exposure and Effect

Cadmium compounds affect many organs and body systems. There is evidence from man or lower animals of effects on the respiratory tract, on the nervous system, on the liver, on formed elements of the blood, on vascular function, on male and female gonads, on thyroids, on pancreata, on bones, and, probably most importantly, on kidney function. In addition, there is evidence that cadmium may cause cancer and birth deformities.

(a) Respiratory Tract Effects

In the respiratory tract, irritation of the nasal mucosa with partial or total loss of the sense of smell has been observed in association with cadmium and nickel exposure[55,65,78] but, at least in one case,[79] there was a loss of sense of smell without evidence of exposure to airborne nickel in a zinc

refinery. Thus, it seems appropriate to conclude that exposure to cadmium compounds, albeit at high concentrations, can cause partial or total loss of the sense of smell. Whether this is due to olfactory nerve damage or to a more local effect is not clear. However, as was mentioned previously, Vorob'yeva[116] found increased chronaxy of the sensory nerves of the skin and the optic nerve in workers exposed to dusts of cadmium oxide.

Exposure at high concentrations has caused acute, fatal, pulmonary edema.[42-50] Lethal exposure levels have been estimated at 2,500-2,900 mg-min/cu m.[44,51,52] This is equivalent to 5-6 mg/cu m for an 8-hour day. Several epidemiologic studies[55,62,116] have reported workplace environmental concentrations well in excess of this concentration, without deaths. It may be that workers were not exposed to cadmium at such high concentrations for more than brief periods, and, since many of the measurements were based on area samples, that workers may not have been exposed at these concentrations at all. Or the discrepancy may in part be explained by different acute toxicities of fumes and dusts, since the latter studies[55,62,116] involved dust exposure. It is concluded that exposure at Ct's (product of concentration and exposure time) of around 2,500 mg-min/cu m may cause acute effects and should be prevented. The main relevance of this conclusion to an occupational standard for cadmium is to the development of a ceiling concentration and to work practices for operations generating large quantitites of cadmium oxide fume, such as brazing with cadmium-containing alloys.

There is considerable evidence of chronic obstructive pulmonary disease (emphysema) from prolonged exposure of workers to cadmium compounds.[34,53-56,58,59,126,127] In Friberg's comprehensive study of nickel-cadmium battery workers, published in 1950,[55] mean values from spirometric tests and spirometric measures in individual workers showed changes attributed to emphysema. While these effects could have been attributed to either nickel or cadmium, Friberg concluded, in part from his animal tests, that, although either nickel or cadmium was capable of causing emphysematous changes, cadmium was more potent in this respect than nickel. Baader[58] confirmed many of Friberg's findings in a German nickel-cadmium plant, but reported his findings in less detail. Bonnell[34] found some workers with sufficient obstructive lung disease to require hospitalization for shortness of breath; these workers were exposed to cadmium oxide fumes. Kazantzis[126] confirmed by spirometry that many of the workers in this plant had reduced pulmonary function, primarily in the time constant of the vital capacity curve. In those workers in this plant exposed for more than 10 years, Buxton [127] found significantly increased residual air volume and residual quotient, consistent with Friberg's observation[55] of a significant increase in residual quotient. Other epidemiologic studies, including recent ones from Belgium,[133-135] continue to confirm the ability of cadmium to cause functional changes consistent with emphysema. This cadmium-induced emphysema may be related to cadmium's ability to inhibit antitrypsin activity.[60]

(b) Blood Effects

Anemia associated with cadmium exposure has been reported in several groups of workers.[38,55,81] A few cases of elevated hemoglobin[44] probably indicate hemoconcentration from acute pulmonary edema. Anemia in experimental animals as the consequence of high doses of cadmium has also been reported,[138-140,143] and appears to be the result of iron deficiency. Elsewhere, cadmium's ability to cause zinc deficiency has been discussed (see Animal Toxicity), but there is only sparse evidence of cadmium's ability to cause iron deficiency, though other mechanisms for production of an iron-deficiency anemia could exist. However, bone marrow changes were not found in 19 workers studied by Friberg.[55] An apparent iron-deficiency anemia could be caused by a deficiency of copper, which is probably carried by the same transport mechanism (thionein) as cadmium. A deficiency of copper would not usually result in a marked alteration of bone marrow but would be evidenced by a normocytic anemia.

(c) Vascular Effects

Perry and Schroeder[83] have presented evidence of increased excretion of cadmium in the urine of hypertensive people, which may suggest that cadmium absorption can cause hypertension, and some experimental evidence from animal studies has supported this suggestion.[88,146-151] This hypertension may be due to cadmium's ability to inhibit utilization of zinc.[88] However, cadmium-induced hypertension has not been confirmed in workers studied[55] or in some experimental animals.[152] The facts implicating cadmium and those absolving it

as a factor in hypertension are impressive. Evidently, more research is needed to clarify the role, if any, played by cadmium in the genesis of hypertension. That one group of workers studied did not have elevated blood pressure[55] when other marked effects (anemia, proteinuria, emphysema, and anosmia) were present suggests that either high doses of cadmium or the presence of cofactors are required, but evidence for this argument is not adequately reassuring.

(d) Pancreatic, Thyroid, and Adrenal Effects

High cadmium levels in pancreata[94,115] and in thyroids[115] from human autopsy material suggest adverse effects of cadmium on these glands. There is limited confirmation of decreases in pancreatic function from animal studies.[230,231] There is also evidence from animal studies [154] that cadmium may increase adrenal activity.

(e) Nervous System Effects

Evidence of an adverse effect of cadmium on the nervous system is sparse. Vorob'yeva[116] found changes in the chronaxies of cutaneous sensory and optical nerves of workers exposed at high concentrations of cadmium. Other reports of fatigue[51] and duodenal or stomach ulcers[79] may conceivably reflect nervous system effects of cadmium, but such an attribution is very uncertain from the data presented. It does not now seem appropriate to conclude that cadmium exposure in the workplace will cause effects on the nervous system, but additional research to clarify this point is needed.

(f) Effects on Bones and Teeth

Bone changes from cadmium absorption have been especially marked in the Itai-Itai episode in Japan.[40,41,89] However, possible contributions by nutritional deficiencies, hormonal imbalance, or other factors seem likely. A group of workers in France also developed osteomalacia after exposure at high concentrations of cadmium,[38] but nutritional deficiencies were probably a contributing factor in these cases, also. There seems little reason to doubt that cadmium absorption was a significant factor, though not necessarily the only factor, in the etiology of osteomalacia in cadmium workers and in people absorbing high amounts of cadmium from pollution of water and resultant pollution of food (the Itai-Itai incidents). However, very high amounts of absorbed cadmium were required to produce the disease, so it is not a probable consequence of exposure to cadmium at concentrations relevant to development of an occupational health standard. Some evidence of carious teeth in association with cadmium exposure was presented by Hardy and Skinner,[81] and there is limited support for this in animal studies.[235] A yellow fringe on the teeth of workers has been observed by several investigators.[62,90] Its cause is not known, but it may reflect deposition of pigment formed from reaction of cadmium with sulfide from decomposition of proteins in the mouth, particularly at the rims of the dental alveoli.

(g) Hepatic Effects

There are a few reports of changes in liver function in cadmium workers.[55,61] Other studies have failed to confirm these findings.[34,54] Fatty infiltration of livers of cats,[80] liver damage in rabbits terminating in cirrhosis,[55] and changes in activities of liver enzymes in rats[234] have been reported as a consequence of cadmium administration to these animal species. Inadequate investigations of hepatic effects in workers exposed at high concentrations and lack of specific hepatic effects at the lower exposure levels, which caused only renal effects or renal and pulmonary effects in more recent studies, are suggested as the explanation for these apparent contradictions, but additional investigations are needed to confirm this suggestion.

(h) Gonadal Effects

Gonadal effects have been repeatedly demonstrated in lower mammals administered cadmium salts.[1 (pp 124-127),91,92,155,166-168] Testicular damage has also been noted in animals (trout) without scrotal testes.[156] Marked necrosis of testes and follicular atresia in ovaries have been consistently found. Repeated administration of cadmium at doses causing significant kidney dysfunction in mice and rabbits[162-164] did not cause testicular effects, indicating that absorption of cadmium in amounts not causing renal effects will not cause testicular changes or, probably, ovarian changes. Ovarian or testicular effects in humans have not been found, but they have not been investigated to a significant extent, probably because of the greater difficulties posed by studies of gonadal function in humans. One investigation[93] of fertility in cadmium workers found one case of impotency with low blood testosterone levels. Kazantzis et al[54] interviewed cadmium workers and took fertility histories, finding no definite evidence of sterility (this point was not further elaborated upon). Smith et al[94] noted high cadmium concentrations in testes of men exposed to cadmium fume. It is concluded that

gonadal malfunction may occur in workers exposed only rarely at sufficiently high concentrations, but it is unlikely that it would occur in concentrations relevant to establishment of an environmental limit, ie, at 100 μg/cu m or below. Methodologic difficulties in studying gonadal function in workers will make needed research in this area difficult. Subjective impressions of workers may add useful information.

(i) Renal Effects

There is a great amount of evidence of the ability of cadmium compounds to cause renal changes. In most cases, this evidence consists of reports of urinary excretion of protein, usually noted as being a low molecular weight protein.[34,54,55,57,61,63-65,76,133,143] In some cases, glucosuria[54,61,71-73] or aminoaciduria[54,71,75] were observed. (The glucosuria may have been the consequence of alterations in pancreatic function,[230,231] though renal dysfunction seems a more likely cause.) More overt evidence of renal dysfunction has also been observed, eg, reduced inulin clearance,[55] reduced urine-concentrating ability,[55,71] changes in the processing of uric acid, calcium, and phosphorus by the kidney,[54,71] and several cases of formation of renal stones.[55,76,77]

Renal dysfunction may be the cause of osteomalacia, though nutritional, hormonal, or thyroid-parathyroid influences may be involved in addition to, or in place of, such changes in kidney function as the adult Fanconi syndrome. Support for the theory that osteomalacia is the consequence of kidney changes comes from a case reported by Adams et al[71] of osteomalacia in a man with a severe defect in tubular reabsorption.

Data on which to develop the mechanism for cadmium-induced renal injury and on the detailed nature of the renal injury have not been presented in this Chapter. It seems evident that the primary effect is a decrease in tubular reabsorption of low molecular weight proteins, with a lesser effect on glomerular filtration, perhaps as a sequel to tubular malfunction. Friberg and coauthors have presented a detailed review of this[1 (pp 105-113)] and their hypothesis is recommended as the most useful explanation based on evidence so far available: ". . . cadmium is probably transported to the tubules bound to the low molecular weight protein, metallothionein. During normal conditions this protein will be reabsorbed in the tubules just as other proteins, and cadmium will accumulate in the renal tissue. Cadmium excretion in 'normal' people and in workers with short periods of exposure to low air concentrations of cadmium thus is low because proteins are almost completely reabsorbed. With increasing exposure more cadmium than can be bound by metallothionein will eventually be accumulated in the kidneys. Cadmium will then exchange with zinc in enzymes necessary for reabsorption and catabolism of proteins. . . As a result of these anti-enzymatic actions less protein will be catabolized or reabsorbed, causing tubular proteinuria. Cadmium excretion will increase also as less metallothionein will be reabsorbed. At this stage the accumulation rate of cadmium will become slower, but cadmium will still be reabsorbed and cadmium levels in the tissue may get still higher. The reabsorption defect will be greater and eventually renal cadmium will cease to increase. Tubular cells will be damaged by cadmium, and it is conceivable that cadmium will be excreted together with desquamated tubular cells, resulting in a decrease in renal levels of cadmium. If glomerular function is impaired, there will also be less filtration of metallothionein."

It is apparent that urinary excretion of low molecular weight proteins and perhaps also urinary excretion of glucose or amino acids constitute early evidence of altered tubular function. This evidence does not usually appear until some time after exposure at sufficiently high cadmium concentrations has started. Tsuchiya[63] found no proteinuria in men exposed at an average of 125 μg/cu m for less than 9 months, and workers with more than 5 years' experience had the highest urine protein levels. Kazantzis et al[54] noted that duration of exposure was important in the development of proteinuria; there were no workers with proteinuria in the group with less than 2 years' exposure, there were 3 workers with proteinuria in the group of 4 exposed 12-14 years, and all workers exposed more than 25 years had proteinuria. Friberg[55] found proteinuria only in those workers with more than 9 years of exposure; had more sensitive methods been used, he might have been able to demonstrate protein in urine after shorter periods of exposure. Tsuchiya[130] concluded, on the basis of a reexamination of workers previously studied[63] and found to have proteinuria, that proteinuria is reversible in some workers (probably those with proteinuria of shorter duration). Thus, testing of workers' urine at frequent

intervals should enable early detection of absorption of toxic levels of cadmium in time to take preventive measures that will prevent the development of serious kidney damage and, if the tubular changes can be reversed, that will enable the organism to correct the early malfunction in the tubules.

Monitoring of blood and urine cadmium do not, on the basis of available evidence, give sufficiently advanced warning of kidney dysfunction. It appears that urine cadmium may rise gradually as undue cadmium absorption continues, but does not rise markedly until more severe, probably irreversible, kidney injury has occurred. After marked kidney injury and marked increase in cadmium excretion has occurred, kidney cadmium levels may decrease significantly. This is taken into account in the hypothesis of Friberg et al quoted above and is exemplified by the finding of Lauwerys et al[133] that workers with severe proteinuria had high cadmium levels in their urine. A more detailed review of the possible significance of cadmium in blood and urine has been presented by Friberg and coauthors.[1] (pp 55-59, 65-72)

(j) Cancer

There has been much interest in the possibility that cadmium exposure may cause cancer, but the issue remains in doubt. Cadmium can clearly cause injection-site sarcomas in rodents[182-187] as well as testicular tumors from sc injection in another area.[188] Development of injection-site and testicular tumors could be prevented by injection of zinc salts.[188] However, injection-site sarcomas in rodents are not indicative of risk of cancer in man (except, perhaps, by injection). The testicular tumors are probably the consequence of hyperplasia and metaplasia from tissue regeneration following extensive tissue damage in the testes from absorption of cadmium. Experimental studies in rodents administered cadmium by long-term feeding[192] did not develop a significantly increased incidence of cancer, but feeding levels may have been too low to allow detection of an increased incidence of neoplasms. Similarly, the investigations of prostate cancer in rats and mice, [105-107] although negative, used dose levels that did not produce other significant evidence of cadmium toxicity and, hence, are not conclusive.

There have been several suggestions of an increased incidence in prostate cancer in cadmium workers.[65,71,96,97]. The replication, at least partial, of the population studied (British battery workers) in three of these reports[65,71,96] should be noted. Credence to only one of them, however, at least raises suspicions of a role by cadmium in the pathogenesis of some cases of prostate cancer. In addition, Lemen et al[97] found 4 cases of prostate cancer among 92 deaths in a study of mortality among 292 workers at a US smelter. The small number of cases in this report as well as the advanced ages of most of the men in all of the mentioned reports makes the argument that cadmium causes prostate cancer less persuasive than is desirable for firm conclusions. The high incidence of prostate cancer, at least histologically demonstrable prostate cancer whether in situ or invasive, in older men complicates the problem of settling etiologic relationships. Moreover, the men developing prostate cancer in British battery factories[65,71,96] were also exposed to nickel.

Lemen et al[97] also found an excess in total neoplasms, mainly in lung cancer, in this same population of workers at a smelter. NIOSH has previously concluded that inorganic arsenic causes a significant excess of cancer, especially lung cancer, based on a review[237] of epidemiologic studies of various populations including smelter workers. Whether exposure to arsenic at concentrations as low as 1 μg/cu m would cause lung cancer is not known; but it also isn't known whether past exposure concentrations had been low. Thus, the role of cadmium in the production of lung and other cancers in the population studied by Lemen et al is not clear. Kipling and Waterhouse[96] surveyed 248 cadmium oxide workers, and found no excess of bronchial carcinoma in this group. The number of the original group still alive was not stated except that it was mentioned that 30 of the 248 were still working.

A summary of the data of Kipling and Waterhouse and of Lemen and associates is presented in Table III-2.

(k) Reproductive Effects

Birth deformities in children of cadmium workers have not been studied, except in a study from the USSR where several children of female cadmium workers were found to have rickets or dental troubles. The number of such deformities was small and details important to an evaluation of the report are lacking, but the implication of the study, ie, that cadmium may be a teratogen, is supported by experimental investigations in

rodents.[95,170-178] Most of the abnormalities in rodents could be classified as delayed or erroneous ossification, such as spina bifida, facial and skull abnormalities, tail abnormalities, and defects in or absence of limbs. Development of cadmium-induced fetal aberrations could be completely prevented by injection of Zn(II) at the time of, or soon after, injection of Cd(II).[177,178] Thus, it is likely that cadmium's ability to inhibit zinc utilization is the cause of most or all of the teratologic effects observed, and that, if cadmium absorption were reduced sufficiently so that zinc utilization were not interfered with, cadmium would not be teratogenic. It should be noted, also, that in a reproduction study[179] involving several generations of rats teratogenic effects were not found.

Studies of whether cadmium is mutagenic are inadequate. Indications that Itai-Itai patients had an excess of chromosomal aberrations[112] were not confirmed in another study of Itai-Itai subjects,[111] involving a small population, however. In the same study,[111] Swedish battery workers exposed to cadmium were found to have a lower incidence of chromosomal changes than controls, but again the population studied was small. The significant difference between the chromosomal aberration rates in Swedish and Japanese persons in this study[111] is a curious but unexplained point. Another study[114] also found chromosomal anomalies in workers exposed to cadmium, but these workers were also exposed to lead and some to zinc in addition to cadmium and lead. Studies of dominant lethal mutations in mice[180,181] indicated that cadmium was not mutagenic by this test. In addition, male mice and their male first-generation offspring did not have aberrations in spermatocytic chromosomes.[181]

(l) Effects on Smokers

Several studies of the effects of cadmium on smokers as compared with nonsmokers have been conducted.[131-135] As would be expected, pulmonary function is poorer in smokers than in nonsmokers exposed to cadmium.[135] An additive rather than a potentiating effect seems more likely from the limited data. Smokers also had a higher incidence of proteinuria than did nonsmokers in a cadmium-exposed population in a Swedish battery factory.[132]

In addition, blood cadmium levels were higher in smokers than in nonsmokers exposed to cadmium in the workers studied by Piscator et al.[131]

(m) Sex Differences

Several workplaces have partially or completely replaced their male work force with women, so that comparative studies of the two groups of work populations might reveal something about differences in sensitivity to cadmium due to sex. However, with the replacement of male workers with women, control measures to improve workroom hygiene have also been instituted. Thus, the apparently greater resistance of women to cadmium, evidenced by fewer effects in women than in men previously employed in the same workplace, is probably due to the lower concentrations of cadmium aerosols to which women were exposed. For example, Piscator et al[131] studied women workers, most of whom worked in the plant previously populated by the men studied by Friberg,[55] and found significantly fewer effects than in the men studied previously; in fact, it is doubtful that his population was adversely affected at all. However, concentrations to which the women were exposed were significantly less (under 100 μg/cu m) than those of the male workers (3-15 mg/cu m), who developed many toxic effects, including emphysema and renal dysfunction. Tsvetkova[95] studied female workers in a plant where concentrations of cadmium were reportedly 0.1-25 mg/cu m; she found no effects in the workers (although she observed rickets and dental troubles in offspring), but it is not evident that she investigated such effects as those on the pulmonary and renal apparatus. Lauwerys et al[133] found no adverse effects in female workers but did observe evidence of altered pulmonary and renal function in male workers. However, the female workers were exposed at 31 μg/cu m whereas male workers were exposed at higher concentrations (66 μg/cu m and higher).

Tsuji et al[79] did not present environmental exposure data, so it is not clear whether their male and female workers were exposed at the same concentrations. If they were, a conclusion that the male and female workers did not differ significantly in sensitivity would be warranted. There was a 14.7% incidence of proteinuria in their male workers and 15.5% in female workers; there was a 7.8% incidence of glucosuria in male workers and a 1.4% incidence in women, based on measurement by test tape, which may be an inadequately sensitive method.

(n) Quantitative Relationships

Table XIV-2 shows toxic effects noted at various exposure concentrations in some epidemiologic studies. The concentration levels shown in the table are frequently oversimplifications of what was found in the environmental surveys, especially at the higher concentration values, and the discussion of the individual papers in *Epidemiologic Studies* should be consulted for a more thorough discussion of environmental concentrations found. It is nevertheless evident that environmental exposure levels of several tenths of a milligram of cadmium/cubic meter have usually resulted in emphysema and proteinuria and, often, in other effects such as anemia, anosmia, and a yellow fringe on the teeth. Changes in the respiratory system have not been reported at exposure concentrations less than 100 μg/cu m, except in groups studied by Lauwerys et al.[133,134] One of these groups[133] of workers, exposed at 66 μg/cu m, had a mean reduction in pulmonary function; however, some of these workers were reported to have been intermittently exposed to cadmium fume at unstated concentrations. It may be that they were exposed to fume at higher levels and that their pulmonary function results heavily weighted the average values. Fifteen of the workers in this group had proteinuria, so that only a few of these cases of proteinuria could be attributed to the additional fume exposure. The fact that all the workers in this group had been exposed to cadmium for from 21 to 40 years is probably significant, in that length of exposure is probably an important factor in development of cadmium toxicity. Taking these and other data into account, Lauwerys and coworkers recommended a workplace environmental limit of 50 μg/cu m, the same as the previous recommendation of Tsuchiya.[63]

There is some evidence of proteinuria in workers exposed to cadmium at concentrations less than 100 μg/cu m. As mentioned above, Lauwerys et al[133] found proteinuria in workers exposed 21 years or more at 66 μg/cu m. In another study by Lauwerys et al,[134] both proteinuria and slight but significant reductions in pulmonary function occurred in workers exposed at concentrations stated to be below 90 μg/cu m. The incidence of renal effects in this group was 9% in the group exposed for less than 20 years and 64% in the group exposed for more than 20 years.

In the population described by Piscator et al[131] there were no significant findings except an increase in haptoglobin in two groups classified by age. One elderly woman who had been classified as a suspect case in 1969 had proteinuria when airborne cadmium concentrations may have been higher. One control also had proteinuria, attributed to a bacterial infection of the tubules.

A striking demonstration of the effect of the concentration of airborne cadmium on renal disease is given by the two reports of Tsuchiya[63,130] describing workers in one plant, studied 10 years apart. In the earlier report,[63] environmental concentrations were around 125 μg/cu m and anemia (attributed in part to inadequate nutrition[130]) and proteinuria occurred in these workers. In his second survey,[130] Tsuchiya found some improvement in the condition of workers who had been examined in the previous study, and found no effects in workers who replaced those leaving employment after the first study. Environmental levels in the later report were reported to be 16-29 μg/cu m with higher concentrations for part of the time.

Thus, an environmental limit that will protect against the development of chronic obstructive pulmonary disease and against renal lesions as evidenced by low molecular weight proteinuria should be sufficient to protect against all toxic effects of cadmium with the possible exception of development of deformed offspring or neoplasms, if these are consequences of cadmium exposure.

Friberg and coauthors[1] (*pp* 79-80, 197-201) have discussed mathematical models for accumulation of cadmium in the renal cortex. Based on an accumulation model involving a simple logarithmic curve, they calculated the following exposures that would result in reaching the threshold of renal cadmium for renal injury: for occupational exposure, 30 μg/cu m in 10 years; for food intake, 0.4-0.6 μg/g wet weight; for community air (ie, continuous) exposure, 1-2 μg/cu m in 50 years; and from smoking alone, more than ten packs of cigarettes/day. However, various assumptions of uncertain validity are required for these calculations, and different assumptions could lead to different conclusions. Among these assumptions are pulmonary absorption, excretion rate, biologic half-time in the renal cortex, and kidney weight. The critical assumption is that the threshold cadmium concentration in the kidney cortex is 200 μg/g wet weight, and, while there are insufficient data on which to validate this assumption, it seems that this threshold concentration probably lies between 100 and 300 μg/g.

TABLE III-1

DESCRIPTION OF POPULATION EXPOSED TO CADMIUM

Group	Airborne Cd, μg/cu m		Population	Length of Exposure, years	
	Total	Respirable		Range	Average
E1	31	1.4	31 Women	1-12	4.1
E2	134	88	27 Men	0.6-19.7	8.6
E3	66	21	22 Men*	21-40	27.8

*Four of these men were also exposed intermittently to cadmium fumes.

TABLE III-2

SUMMARY OF CANCER MORTALITY DATA OF KIPLING AND WATERHOUSE[96] AND OF LEMEN ET AL[97]

Cancer Site	Number of Cases		Probability of Chance Occurrence
	Expected	Observed	
Kipling and Waterhouse*			
All sites	13.13	12	Nonsignificant
Bronchus	4.40	5	"
Bladder	0.51	1	"
Prostate†	0.58	4	0.003
Testis	0.11	0	Nonsignificant
Lemen et al*			
All sites	17.51	27	0.05
Respiratory system	5.11	12	0.05
Digestive system	5.78	6	Nonsignificant
Prostate§	1.15¶	4	"
Other unspecified	6.62	9	"

*Environmental data were not presented by Kipling and Waterhouse. In a 1973 industrial hygiene survey of the smelter studied by Lemen et al, most concentrations of cadmium were below 1 mg/cu m, but they ranged up to 24 mg/cu m; there were also low concentrations of arsenic found (about 1 μg/cu m).

†The ages at death of 3 of these 4 men were given by Potts[65] as 65, 65, and 75.

§The ages at death of these 4 men were 64, 71, 77, and 79.

¶If the comparison between observed and expected cases of prostate cancer deaths is limited to those who lived at least 20 years since their first exposure, the expected number is 0.88, which is significantly different from the 4 observed cases at $p<0.05$.

IV. ENVIRONMENTAL DATA

Environmental Concentrations

Concentrations of airborne cadmium fume or dust in workplaces, as cited in the literature, are related mainly to reports of toxicity of cadmium. Ideally, such reports would give concentrations at worker breathing zones, averaged over the period of exposure. Size distribution, temporal variation, and chemical composition would be stated. In none of the reports are such ideal data presented. Samples obtained from fixed-position air sampling devices are more common than breathing zone samples. Many of the reports antedate the development of reliable personal samplers.

Particle sizes of freshly formed fume are ordinarily in the tenth-to hundredth-micrometer range. The workroom studies in which particle size has been estimated confirm this for cadmium fume. Neumann[238] reported that concentrations determined by electrostatic precipitator sampling were 65 times those determined by impinger sampling, typical of a particle size well under 0.5 μm. King[128] reported 91% by weight of a cadmium fume to be less than 0.5 μm.

Table XIV-2 shows some toxic effects in association with ranges of airborne cadmium concentrations. As the table shows, cadmium concentrations have ranged to very high levels.

Air Sampling

The most popular current method for taking air samples for cadmium is the use of cellulose ester membrane filters. Such filters having a nominal pore size of 0.8 μm will provide essentially complete collection for particulates in the size range of fume, less than 0.5 μm, or the larger particle sizes of dust.[239,240] If lower resistance to airflow is necessary, membrane filters with nominal pore sizes up to 5.0 μm may be used but possibly with some loss in efficiency. Other ashless filter papers may be used, but analytical filter papers such as Whatman 41 have efficiencies which vary greatly with face velocity, and microsorban is not as convenient or as readily available. Nuclepore filters are not sufficiently efficient at fume particle sizes,[241] and glass fiber filters, though otherwise useful,[242] cannot be digested by the recommended analytical procedure. Electrostatic precipitator samples are satisfactory for general air sampling, but inconvenient for breathing zone samples.

Size-frequency determinations of airborne cadmium may be useful in evaluating the degree of potential absorption. Several cascade impactors are available for air sampling which could be suitable for particle-size frequency determination if followed by a membrane filter.[243] Heavy stage deposits should be avoided to prevent reentrainment of deposited particles. An alternative for determination of particle size frequency over longer time periods is the multiple cyclone sampler.[244] Optical or electron microscope size-frequency determination is probably of little value at hygienic concentrations, because the cadmium dust or fume cannot be readily distinguished from other dust in polluted air. Light-scattering electronic particle counters are similarly nondiscriminatory.

Air sampling for worker exposure should be performed by personal sampling whenever possible. A personal sample can be taken for up to 8 hours on a worker by using a battery-operated, belt-worn pump connected by rubber or plastic tubing to a membrane filter holder. Any known flow rate between 0.5 and 3 liters/minute is satisfactory. To obtain TWA exposures, personal samples should be taken for a minimum of 2 hours. If sampling is conducted for less than a full work shift, all operations likely to generate cadmium dust, fume, or mist must be included within the sample period.

As an often less desirable alternative to personal sampling, "breathing zone" samples may be taken through a filter or precipitator tube held near the

worker's face. If TWA concentrations are to be estimated, there should be at least 3 samples at the site of each task performed by the worker. The average concentration of airborne cadmium for each task is then multiplied by the number of hours the worker engages in that task; the concentration-time (Ct) products are added up and divided by the number of hours in the working day.[245] Alternatively, Ct products can be added and divided by total sampling time.

General air samples are often desirable to monitor effectiveness of control procedures. Such samples should be taken at specified locations so that control procedure effectiveness may be determined by before-and-after comparisons.

Chemical Analysis

Cadmium level is readily determined in an aqueous matrix by a variety of techniques. Analytical procedures include electrochemical, [246,247] spectrographic,[246] colorimetric,[246,248,249] and atomic absorption[110,242,250,251] techniques. These methods have been compared by Cholak and Hubbard[246] and by Matson et al.[252]

All of the methods noted above require that the sample be dissolved in an aqueous medium. This can be accomplished by a variety of techniques. Oxidizing acids, such as nitric acid, [246,248,249] perchloric acid,[252] or mixtures of acids, [250] have been used. Ashing in a muffle furnace may give variable results because of the volatility of cadmium and certain of its salts. Low temperature ashing has also been used.[242]

The colorimetric method using diphenylthiocarbazone (dithizone) has been employed.[246,248,249] The procedure described by Saltzman[249] uses a buffer system at high pH. This matrix maintains a homogeneous aqueous system prior to the extraction step. The reagents also mask the reaction between certain metals and dithizone.

Spectrographic techniques have been used extensively.[248] Air quality data have been compiled using this method of analysis.[13,242,253] This method has desirable attributes, particularly for analysis of several elements in a sample.

Electrochemical analysis using stripping techniques[252] provides greater sensitivity than some of the earlier techniques.

Atomic absorption spectroscopy has received wide acceptance. Homogeneous solutions with aspiration rates which can be matched with those of standards are readily analyzed at low concentrations. Interferences by both phosphate[110] and sodium chloride[1 (p 5),254] have been reported. It does not seem likely that these interferences will be significant in analyzing most samples of airborne cadmium, but, if they are significant, the samples can be treated as described in the discussion (see below) of analysis of blood and urine, where such interferences can be significant. The cadmium can be chelated and the chelate complex extracted in an organic solvent for analysis. The flexibility which atomic absorption analysis has for the analysis of a number of metals is a considerable advantage, because the preparation steps are similar. Trace metal analysis requires a highly skilled technician, regardless of the specific technique used. Meticulous cleanliness and attention to detail are needed to prevent loss or contamination.

A method is presented in Appendix II for the analysis of air samples. Atomic absorption spectroscopy is recommended because of the precision, accuracy, and sensitivity attainable; an additional advantage is the flexibility of analysis which this technique provides. This technique is used in several laboratories for the analysis of air samples.[242,251,255]

A similar procedure for the determination of cadmium in air was developed by the Physical and Chemical Analysis Branch of the National Institute for Occupational Safety and Health (NIOSH). The test of the NIOSH procedure included studies of the variation of hot-plate temperature, quantity and quality of nitric acid (57% increase in acid volume, acid not redistilled), loss of cadmium by prolonged heating or heating to dryness, the use of hydrochloric acid for achieving final working solutions, the use of a water blank, and the variation in band pass of the spectrophotometer. The standard deviation of 7 replicates was less than 3%. Two spectrophotometers gave similar results.

Lehnert et al[256] have described a method of analysis of blood and urine for cadmium by atomic absorption spectrophotometry after extraction by methyl isobutyl ketone of a chelate of cadmium and ammonium pyrrolidine dithiocarbamate. Wet ashing of 10 ml of serum or 50 ml of urine was accomplished with a solution of 10 ml of 65% nitric acid, 5 ml of 96% sulfuric acid, and 5 ml of 70% perchloric acid. Residues were dissolved in dilute hydrochloric acid and adjusted to pH 2.5. The

chelate was formed by adding 2 ml of 5% aqueous ammonium pyrrolidine dithiocarbamate solution, and was extracted into 2 ml methyl isobutyl ketone. This organic phase was then analyzed by atomic absorption spectrophotometry. Under their conditions, they found detection limits of 12 ng Cd/100 ml of urine or 60 ng Cd/100 ml of serum, with a precision of 10% and mean recoveries of 96%. Using this method, Lehnert et al[120] found mean blood and urine concentrations of cadmium in 15 adults not exposed to cadmium in their work to be 0.33 μg Cd/100 ml of serum and 84 ng Cd/100 ml of urine, based on 24-hour urine samples. Berman [110] described a similar procedure for atomic absorption spectrophotometric analysis of blood and urine, except that blood proteins were first precipitated with trichloroacetic acid before the chelation and extraction. Imbus et al[121] used a modification of the spectrographic method of Cholak and Hubbard[246] to analyze blood and urine of about 150 workers, mostly from Cincinnati but also from other cities in the US, apparently not exposed in their work to cadmium or the other metals examined. Cadmium was removed from blood or urine samples by dithizone, then removed from the dithizone solution by 0.2 N hydrochloric acid. After evaporation to dryness, the material was dissolved in buffer and analyzed spectrographically. Mean blood concentrations were 0.85 μg/100 g, with 95% of the samples being less than 1.68 μg/100 g. Mean urine concentrations were 1.59 μg/liter, and 95% of the determinations were less than 4.13 μg/liter. The ranges were 0.34-5.35 μg Cd/100 g of blood and from less than 0.5 to 10.8 μg Cd/liter of urine. These concentrations are in the general range of those found by Lehnert et al[120] on German adults, viz, means of 0.33 μg/100 ml of blood and 0.84 μg/liter of urine.

Pulido et al[254] corrected for the absorbance of chloride ion at the cadmium 2,288 Angstrom line by using a uniformly shaped flame such as that produced by a ring burner and by a reduction in slit width. They also found they could correct for chloride interference by comparing absorbances from a continuous source such as a hydrogen lamp with that of the cadmium hollow cathode tube.

Matson et al[252] have reported that use of anodic stripping voltammetry gives results and precision similar to those of atomic absorption spectrophotometry, neutron activation, dithizone colorimetry, and emission spectrography for analysis of 1-500 ng quantities of blood, hair, or urine.

Recent developments in analysis of cadmium in food, urine, blood, tissues, water, and air have been reviewed by Friberg et al.[2] (*pp* 2-1 *to* 2-17)

Procedures for the determination of urinary proteins are discussed in Appendix III.

Engineering Controls

In a striking instance of control, airborne cadmium concentrations were reduced by a factor of over 1,000 in vacuum metalizing.[257] Less striking reductions were observed in operations between metalizing cycles. A reduction by a factor of 10 in cadmium dust during battery manufacture was noted.[55] In both the examples cited above, conventional ventilation techniques were used for control. Control measures for powder-handling operations with both moderately toxic and very toxic materials, applicable as criteria in designing engineering controls for a number of cadmium- generating operations, are given in *Industrial Ventilation*.[258] Local exhaust ventilation should be provided at all operations as shown in this manual. Inasmuch as cadmium is more toxic than most of the other materials handled, enclosure should be maximized and the upper parts of ranges of air turnover rates should be used.

Air volumes tabulated for welding[258,259] are calculated for a control velocity of 100 feet/minute (fpm). For cadmium fume, control velocities of 150 fpm should be used, so that volumes 50% greater than the tabulated volumes should be used.

Local exhaust systems should be designed and operated in conformance with the American National Standard *Fundamentals Governing the Design and Operation of Local Exhaust Systems*, Z9.2-1971.[260]

Published designs for ventilation control[258] are illustrative of approaches which have been successful in certain applications. It should be emphasized that the recommendations on environmental limits are for performance. Any method of meeting these recommendations consistent with the health and safety of workers may be acceptable. In each case, success of control measures must be demonstrated by appropriate air sampling.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1941, the American Standards Association (now known as American National Standards Institute, Inc., or ANSI) recommended as an American Defense Emergency Standard an allowable concentration of 1 mg Cd/10 cu m (0.1 mg Cd/cu m) for cadmium and its compounds.[248] This was superseded in 1970 by ANSI Z37.5-1970,[261] which recommended a TWA concentration of 0.1 mg/cu m and a ceiling concentration of 0.3 mg/cu m for cadmium fume and a TWA concentration of 0.2 and a ceiling concentration of 0.6 mg/cu m for cadmium dusts as acceptable concentrations during an 8-hour workday. In the case of workdays longer than normal, the standard recommended that exposures not exceed Ct values (the product of concentration and time) of 50 mg-min/cu m for fume and 100 mg-min/cu m for dusts; this is approximately equivalent to maintaining the same TWA concentrations calculated for workdays greater than 8 hours. Although the report briefly reviewed cadmium toxicity, the specific basis for the acceptable concentrations was not stated.

This ANSI standard[261] is the basis for the present federal standard (29 CFR 1910.1000) of 0.1 (TWA) and 0.3 (ceiling) mg Cd/cu m for fume and of 0.2 (TWA) and 0.6 (ceiling) mg Cd/cu m for dust, published in the *Federal Register* 39:23543 (Table G-2), June 27, 1974 (with an erroneous listing of 3 instead of 0.3 mg/cu m as the ceiling for fume).

In 1946, the ACGIH recommended an MAC Value of 0.1 mg/cu m for cadmium, continuing it for several subsequent years but changing the name MAC Values to Threshold Limit Values (TLV's) in 1948 (these 1946-1949 MAC or TLV lists were unpublished but privately circulated). In 1956,[262] the TLV of 0.1 mg/cu m was assigned to CdO fume, rather than Cd. In 1965,[263] a tentative value of 0.2 mg/cu m for cadmium (metal dusts and soluble salts) was added, and changed to a recommended value in 1967.[264] More recently, the ACGIH recommended several changes in the TLV's of cadmium dusts and fumes. In 1970, the TLV of cadmium dusts and salts was continued at 0.2 mg/cu m as a TWA concentration but the TLV of fume was changed to 0.1 mg/cu m as a ceiling.[265] In 1973, the ACGIH announced its intent to change the TLV of fume to 0.05 mg/cu m, also as a ceiling.[266] In 1974, the intention to change the TLV of cadmium dusts and salts to 0.05 mg/cu m as a TWA concentration was announced. [267] In 1975, a note was added indicating that cadmium oxide production involved a carcinogenic or cocarcinogenic potential.[268] In a supplement[269] to the 1971 TLV documentation,[270] a review by Bonnell[271] and the report of Tsuchiya[63] were cited as reasons for a lowering of the TLV of cadmium fume to a ceiling concentration of 0.05 mg Cd/cu m. The basis for indicating that there is a carcinogenic or cocarcinogenic potential in cadmium oxide production was not stated.

According to Riihimaki,[3] the occupational health environmental limit of Finland was changed several years ago to 20 μg/cu m for cadmium dusts and 10 μg/cu m for cadmium fumes. He did not give the basis for these limits.

Sweden[272] has promulgated limit values of 0.05 mg Cd/cu m (total) and 0.02 mg Cd/cu m (respirable), as TWA concentrations for cadmium and its inorganic compounds. The basis was not stated, but a discussion by Friberg et al[1] (p 200) suggests that these limits are based in part on the mathematical model discussed in Chapter III, *Correlation of Exposure and Effect.*

In a comparison of USSR and US hygienic standards, Roschin and Timofeevskaya[273] reported in 1975 that the USSR maximum permissible concentration (a ceiling value) for cadmium oxide was 0.1 mg/cu m, but they did not describe the basis for this limit value.

Many other countries have also adopted 0.1 mg/cu m as the permissible limit of cadmium or cadmium oxide. According to a 1970 report of the ILO/WHO,[274] these include Bulgaria, Czechoslovakia, Hungary, Japan, Poland, and Rumania.

Basis for the Recommended Environmental Standard

(a) Workplace Environmental Limits

In Chapter III (see *Correlation of Exposure and Effect*), various chronic effects of exposure to cadmium were discussed. Clearly demonstrated effects include anemia, kidney malfunction, and pulmonary changes including emphysema; less clearly demonstrated effects or effects with less evidence of relevance to a workplace environmental standard include effects on gonads, adrenals, pancreas, thyroid, and liver. Conflicting evidence of changes in liver function may be accounted for by differences in examination of liver function in the various studies or by the likelihood that liver function is adversely affected only at high exposure concentrations. Both possible explanations may be correct, so that effects on the liver may occur after sufficient exposure to cadmium.

Except for the study of Tsuchiya,[63] anemia has not been observed in workers except from exposure at high concentrations. Tsuchiya observed anemia in workers exposed at an average concentration of 125 μg/cu m. However, in a later study of workers in this same plant,[130] he commented that the anemia might have been due in part to nutritional deficiencies; in any case, it did not occur in workers whose exposure levels were reduced, eventually reaching 16-29 μg/cu m after engineering controls had been improved.

While it seems likely that the threshold for development of adverse effects on pulmonary function is higher than the threshold for adverse effects on kidney function, available data do not clearly establish this. Lauwerys et al[133] found reduced pulmonary function and proteinura in workers, all smokers, exposed to cadmium at concentrations of 66 μg/cu m, thought to represent past exposure also, for up to 40 years; some of these workers were also occasionally exposed to cadmium fume (most likely cadmium oxide fume). Only proteinuria was seen in workers exposed 1-12 years at 134 μg/cu m.

While these findings could reflect the longer period of time required for the development of emphysema, it was noted that there were decreases in pulmonary function measurements that were not statistically significant in the workers exposed at 134 μg/cu m. It seems that if emphysema were going to develop in these workers a reduction in pulmonary function should have become more evident. Tsuchiya[63] did not study pulmonary function (but he did not find abnormal chest X-rays), so his finding of proteinuria without emphysema may not support the argument that renal dysfunction occurs at lower concentrations than does pulmonary dysfunction. In view of the less than positive support for this inference on relative thresholds for renal and pulmonary dysfunction, medical examinations of cadmium workers should include studies of both kidney and lung functions (see later discussion of medical surveillance).

Workplace environmental limits of 40 μg Cd/cu m as a time-weighted average concentration and 200 μg Cd/cu m as a 15-minute ceiling concentration are recommended as part of the environmental standard.

Tsuchiya recommended a TWA limit of 50 μg/cu m in his 1967 report[63] but qualified his recommendation with the comment that this limit applied to Japanese workers and not necessarily to others. The nutritional status of these workers may have been a consideration in his qualification of the recommended limit. Lauwerys and coworkers[133] also recommended a workplace limit of 50 μg Cd/cu m, based on findings of no toxic effects in groups of workers exposed at 31 μg/cu m and of toxic effects in workers exposed at 66 μg/cu m or more. Their findings of proteinuria and reduced pulmonary function in workers exposed up to 40 years at 66 μg/cu m suggest that the recommended limit of 50 μg/cu m does not have a large margin of safety. Some of this work force was intermittently exposed to fume, presumably at higher concentrations, but this does not completely explain the effects at 66. Prior exposure concentrations may have been higher, but there is no direct evidence to support such a speculation. The authors commented that they were unsure of concentrations in prior years but had assumed that they were the same because no important process modifications had occurred; however, they considered lack of data on previous exposures to con-

stitute a major uncertainty in their survey. It should be noted that Lauwerys and coworkers,[133] mindful of these considerations, recommended a limit of 50 μg/cu m.

Additional support for this TWA limit of 50 μg/cu m comes from another work population, in this same study of Lauwerys et al,[133] which had experienced no toxic effects at 31 μg/cu m, and from the report of Piscator et al[131] on workers exposed at below 100 μg/cu m, mostly at about 40 μg/cu m. One elderly woman in this latter group of workers had proteinuria, but she had also been found to have proteinuria some years earlier, when exposures were apparently higher. Other significant effects attributable to exposure to cadmium were not found; however, one control had renal disease resembling that induced by cadmium, probably the result of a bacterial infection. The entire population in this study was female, and, as was discussed in *Correlation of Exposure and Effect*, men and women appear not to differ in their susceptibility to cadmium.

However, because of the low margin of safety afforded by a limit of 50 μg/cu m suggested by the proteinuria in men exposed many years at a concentration believed to be about 66 μg/cu m, a more conservative limit of 40 μg/cu m is recommended. This limit offers a greater, and probably sufficient, margin of safety.

An important demonstration of the validity of a limit in the range of 30-60 μg/cu m comes from the two sets of findings of Tsuchiya.[63,130] Workers who had developed anemia and proteinuria at 125 μg/cu m improved when exposure concentrations were gradually reduced to 16-29 μg/cu m and new workers did not develop toxic effects (although, as mentioned earlier, improved nutrition may have obscured the pertinence of the observation of anemia).

Data on which to base a recommended ceiling concentration limit are more contradictory. Evidence of acute pulmonary disease at 2,500-2,900 mg-min/cu m, or about 5 mg/cu m for 8-hours' exposure, seems an appropriate basis for recommending limitation on excursions above the TWA concentration limit. However, other investigations have reported exposure levels up to 25 mg/cu m, [95] up to 24,[116] up to 19,[62] and up to 15,[55] without acute pulmonary disease. While it may be that workers were not exposed at such high concentrations more than briefly or that much of the airborne cadmium was nonrespirable dust, the apparent contradictions cannot be readily dismissed. On the other hand, one study[47,48] indicated the occurrence of acute intoxication from cadmium oxide fume at concentrations estimated to be in the range 10-140 μg Cd/cu m, for a cumulative exposure of almost 10 hours. The great range of concentrations found in this simulation of the accidental exposure makes interpretation of the exposure Ct (product of concentration and exposure time) difficult. In addition, the authors[47] suggested that other fumes (copper and zinc, probably as oxides) and fluoride gases (hydrogen fluoride and carbonyl fluoride) contributed to this poisoning, as well as to another fatal poisoning case they described. Until better and less contradictory information is developed, a ceiling concentration limit is proposed that is based in part on good practice, ie, realistic limitations on excursions, and in part on the belief that acute pulmonary disease, possibly with fatal consequences, can develop at around 2,500 mg-min/cu m.

A ceiling concentration limit of 200 μg Cd/cu m, based on sampling periods of 15 minutes, is recommended. Adherence to this limit would prevent excursions, as averaged over a 15-minute period, more than 5 times the recommended TWA concentration limit. Furthermore, it would limit brief exposures to about 1/100th of that Ct likely to cause serious acute disease, ie, 2,500 mg-min/cu m. If a ceiling limit of 200 μg/cu m on 15-minute sampling were enforced, it would be possible to expose workers for up to 2 hours/day, for 8 15-minute periods, at 200 μg/cu m if there were no exposure for the rest of the day (a concentration of 200 μg/cu m for 120 minutes would give a Ct of 24,000 μg-min/cu m, the same as the TWA concentration of 40 μg/cu m for 600 minutes). This Ct of 24,000 μg-min/cu m is almost 1/100th that of 2,500 mg-min/cu m or 2,500,000 μg-min/cu m.

In addition to these kidney and lung effects of cadmium exposure, there is reason for concern about teratogenic and carcinogenic effects. Experimental evidence of teratogenic effects of cadmium[95,170-178] was developed in rodents given high doses of cadmium compounds, but there is limited confirmation in a USSR study of children of female cadmium workers. Unfortunately, this report gives too few details to allow critical examination. These human fetal abnormalities were

probably the result of retention of zinc by the mother from cadmium absorption, with the consequence that too little zinc was available for fetal development. This is supported by experimental evidence that injection of zinc salt into rodent dams at the time of or soon after injection of cadmium salt prevented the development of abnormalities.[177,178] Thus, reduction of cadmium exposure to a level that does not result in abnormal zinc requirements should allow sufficient zinc to the fetus for normal development. This point involves some unproved assumptions but has some additional support from an analogy with the role of zinc in renal injury (see *Correlation of Exposure and Effect*). Clearly, research on this point is needed.

Evidence of cadmium's ability to cause malignant or other tumors is contradictory. A small number of cases of prostatic cancer have been found among men working with cadmium,[65,96,97] mostly in men in their 7th and 8th decades. Although these few cases do not establish cadmium's ability to cause prostate cancer, some investigators[97] have found statistically significant evidence of an increased incidence of this type of cancer among men who have lived for 20 or more years since their first exposure to cadmium and who were exposed during at least 4 years. Evidence that cadmium does not cause prostate cancer comes from an epidemiologic study[101,102] and from experimental work with rodents.[105-107] However, neither type of investigation has been free of significant flaws. The epidemiologic study[101,102] did not obtain good evidence that the subjects were exposed to cadmium, so it is not appropriate to cite the results as positive evidence that cadmium does not induce prostate cancer or that it does induce kidney cancer, as was discussed in *Effects on Humans*. The rodent studies[105-107] did not use doses of Cd(II) sufficient to cause significant toxicity and, thus, are not helpful.

Evidence of an excess of total neoplasms and of lung cancer among cadmium smelter workers developed in a NIOSH study[97] is difficult to interpret because there was also exposure to arsenic; NIOSH has previously concluded that inorganic arsenic compounds are carcinogenic[237] (although concentrations of arsenic known to have caused a high incidence of lung cancer were higher than those found in 1973 in the NIOSH study). In addition, the study of Kipling and Waterhouse[96] did not find an excess of lung cancer, although lack of detail makes comparison of the studies uncertain. Priority should be given to mortality studies of cadmium workers without concomitant exposure to other toxic materials and to long-term animal studies at doses up to maximally tolerated ones.

In view of the present uncertainties in the evidence on teratogenicity and carcinogenicity of cadmium in occupational exposure, a standard based on these effects is not now recommended. This recommendation should be reconsidered if additional data on these points that warrant such reconsideration are developed.

The recommended limits of 40 μg/cu m (TWA) and 200 μg/cu m (ceiling) are for total particulate cadmium. Thus, limits based only on small, so-called respirable, particles, are not recommended. Cadmium oxide and many other forms of cadmium are not inert, varying in their solubilities in water and probably in body fluids, so that large particles not reaching the alveoli may still be toxicologically active because they can be removed from the upper respiratory tract by ciliary action and transferred to the gastrointestinal tract. Thus, some of these large particles would probably be swallowed and become systemically toxic through gastrointestinal absorption (though gastrointestinal absorption would be expected to be less than absorption from the respiratory tract).

It has been implicit in the environmental limits, such as TLV's that have prevailed for many years (see discussion of previous standards in the section above), that cadmium oxide fume is more toxic than cadmium oxide dust. It seems probable that the basis for this is the assumption that fumes, being usually of smaller particle sizes than dusts, will penetrate more efficiently into the lungs and thus be more efficiently absorbed by the blood. For compliance purposes, it is not evident how to distinguish fume and dust except by particle size, even if there were some more fundamental difference in toxicities of fume and dust. A detailed comparison of results from various epidemiologic investigations is inappropriate because of differences in methods of investigation, in characteristics of the populations studied, including differences in work history, and, perhaps most importantly, in ability to describe exposure levels because of variations in methods and frequencies of estimating concentrations over the years of exposure usually required to cause toxic effects.

Nevertheless, allowing for these difficulties, it seems that a comparison of the results of the studies of Tsuchiya, [63, 130] of Kjellstrom et al,[132] and of Lauwerys et al[133] exemplifies the problem. Workers studied by Tsuchiya[63,130] who were exposed to fume at about 125 μg/cu m developed toxicity, but new workers exposed in the same plant at gradually decreasing concentrations (to under 50 μg/cu m) did not develop toxicity, and the clinical conditions of some of the first group of workers improved. One of the groups investigated by Lauwerys et al[133] at 66 μg/cu m (total) or 21 μg/cu m (respirable) of dust contained proteinuric individuals; it is conceivable that these exposure concentrations had been higher in previous years, as discussed earlier. Kjellstrom et al[132] described a population exposed to cadmium oxide dust that was almost entirely respirable, ie, below 5 μm in particle size; exposure levels of this population had been about 50 μg/cu m recently but had been higher in prior years. Considering the incidence of proteinuria in these populations and making some judgments about differences in overall exposure levels, it seems that the effects found are comparable at similar concentrations of either total dust or fume. While this argument is not a rigorous justification for basing the recommended environmental limit on total particulate, it seems at least to add some support to a limit expressed as total particulate. Perhaps a more important point is that, since data are not available to demonstrate unequivocally that a given amount of cadmium is more toxic as small than as large particles, a workplace environmental limit in terms of total particulate is more conservative, ie, effectively lower, in many situations than the same limit in terms of respirable particulate.

The recommended limits are also proposed to apply to all forms of cadmium. There is limited information that some compounds of cadmium are less toxic than others, but lack of good data on these differences makes difficult a recommendation of several limits for different compounds of cadmium. If exposure to alkyl forms of cadmium is encountered, one could speculate by analogy with alkyl versus inorganic forms of lead or of mercury that the recommended standard will not offer sufficient protection. More research on relative toxicities of various forms of cadmium is needed before different standards for each form can be derived.

(b) Medical Monitoring

It is proposed that mandatory medical surveillance include preplacement and periodic examinations of lungs, kidneys, and blood pressure. In addition, blood counts, studies of liver function, and, in male workers, palpation of the prostate are recommended. Pulmonary function tests should be performed periodically, and chest X-rays should be taken if indicated from results of periodic examinations. For comparison, preplacement examinations and examinations at termination of employment involving cadmium exposure should include X-rays as well as pulmonary function tests. Quantitative analysis of urine protein should be conducted frequently, since this should give early and probably the first indication of adverse effects of cadmium. Proteinuria with its implications of renal dysfunction is less likely to be reversible as it continues, so early detection of low molecular weight proteins in the urine, with the expected result of steps to improve hygiene and work practices, should prevent serious and irreversible effects of cadmium. Therefore, it is proposed that analysis of urine be conducted every 4 months as well as before placement and at termination. Procedures for estimations of proteins in urine are described in Appendix III; the conventional boiling test is not adequate for cadmium-induced proteinuria. If a worker is found to begin to excrete significant amounts of protein in his urine during exposure to cadmium, electrophoretic examination of the urine for the presence of various proteins, especially for peaks in the β-globulin region, will be helpful in deciding whether exposure to cadmium is involved in the genesis of the proteinuria. Alternatively, specific analysis for β_2-microglobulin can be performed. It can be performed by radioimmunoassay or radial immunodiffusion, which give comparable results[275]; semi-automatic procedures allowing simultaneous processing of 24 samples have been described.[276] Piscator[277] has pointed out that an increase in total protein excretion in cadmium workers of 2-3 fold is accompanied by an increase in excretion of β_2-microglobulin of about 50-fold. Analysis of urine for glucose and amino acids is also recommended since in some cases it may give early evidence of renal changes. In this connection, Piscator[74] found that quantitative determination of glucose in urines of cadmium workers showed slight increases in excretion of glucose that were not revealed by test tapes of the type intended for detection of diabetes mellitus.

While the evidence of hypertension from cadmium absorption is contradictory, blood pressure measurements are simple, inexpensive, and harmless and should be part of the required examination.

The uncertain nature of the evidence of liver dysfunction makes a requirement for liver function tests difficult to justify. Similarly, anemia is unlikely at exposure concentrations near the recommended limits. However, both liver function and blood tests are recommended for their possible relationship to cadmium exposure as well as their relevance to an evaluation of general health. A digital prostate examination is also recommended, at least in workers over 40 years old, and can include a rectal examination as part of an evaluation of health status.

Smokers should be counseled on their possibly increased risk of chronic pulmonary disease during exposure to cadmium.

(c) Record Retention

Because of the possible development of chronic obstructive pulmonary disease or chronic renal disease as a result of cadmium exposure, retention of medical and environmental records for 20 years after cessation of work involving exposure to cadmium is recommended.

(d) Biologic Monitoring

Monitoring of blood or urine for cadmium is not proposed as a requirement because blood or urine cadmium concentrations do not adequately correlate with absorption of cadmium or with the state of health of the individual worker. However, group means may correlate better, so such determinations may be useful in assessing plant hygiene and work practices. In addition, gradually increasing levels of cadmium in urine may indicate undue absorption of cadmium that may eventually lead to toxic injury. Thus, periodic monitoring of urine for cadmium is recommended. If the concentration of cadmium in urine of an individual worker rises above the upper part of the range of normal concentrations of urine cadmium, probably about 10 μg/liter,[121] an investigation of such a worker's personal habits and hygiene as well as of his or her occupational exposure to cadmium is suggested. Blood or urine can be analyzed by the method of Lehnert et al,[120,256] described in Chapter IV, *Chemical Analysis*. This and similar methods such as that described by Berman[110] utilize atomic absorption spectrophotometry, so that chloride and other interfering substances must be eliminated, for example by chelation of the cadmium and extraction of the chelate by an organic solvent.[110,120,256]

(e) Environmental Monitoring

Sampling and analysis methods were reviewed in Chapter IV. Cadmium aerosols should be collected on 0.8 μm cellulose filters. While filters of smaller pore size, for example 0.45 μm, will be just as efficient, they place a greater load, possibly too great a load, on the sampling pump. Much larger pore sizes, for example 5 μm, may collect the particulate less efficiently. Atomic absorption spectrophotometry was selected for analysis of cadmium because it is reliable, sensitive, and quick; in addition, it is probably more accurate than other methods, but relative accuracies of various methods have not been adequately studied. Other analytical methods, such as polarographic or colorimetric methods, may be more suitable in specific applications, and they can also be reliable. Recommended procedures for sampling and analysis are given in Appendices I and II.

(f) Work Practices

Work practices are discussed in Chapter VI. Brazing with alloys containing cadmium (often referred to as silver soldering) is especially hazardous because of the high concentration of cadmium oxide fume produced, so good local ventilation and, often, respiratory protection are needed. Storage, handling, and eating of food in cadmium exposure areas should be prohibited to prevent food contamination and subsequent ingestion of cadmium. While cadmium does not pose a fire hazard, its deposition on smoking materials may result in generation and inhalation of cadmium oxide fume at a later time, so that smoking as well as the carrying of uncovered smoking materials in the workplace should be prohibited. There isn't good evidence that cadmium aerosols will penetrate the skin, but their deposition on clothes may result in aerosol generation (eg, blowing of dust) away from work, which may increase the workers' exposure as well as cause his family to be exposed. For this reason, it is proposed that workers be required to change work clothing before leaving work.

(g) Informing Workers of Cadmium Hazards

A continuing education program is an important part of a preventive hygiene program for employees exposed to hazardous materials such as

cadmium. Workers should be periodically apprised by properly trained persons about the possible sources of cadmium exposure, the adverse health effects associated with excessive exposure to cadmium, the engineering and work practice controls in use and being planned to limit exposure to acceptable levels, and on environmental and medical monitoring procedures used to check on control procedures and on health status of employees. The types and functions of monitoring equipment, such as personal samplers, should be explained so that each employee understands his or her part in environmental monitoring. Medical monitoring procedures should be explained, especially the pulmonary function and urine protein studies, and their importance in detecting possible adverse health effects from cadmium exposure discussed. The suggestive evidence of prostate cancer from cadmium exposure should be mentioned so that male workers will understand the reasons for periodic rectal examinations. The benefits to workers of participating in these environmental and medical monitoring procedures should be stressed.

(h) Action Level

It is recognized that many workers are exposed to small amounts of cadmium compounds or are working in situations where, regardless of amounts used, there is only negligible contact with the material. Under these conditions it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily to protect workers' health under more hazardous circumstances. Concern for workers' health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, an action level of cadmium has been defined as occupational exposure above half the recommended TWA environmental limit, thereby delineating those work situations which do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. This level has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, brazing, welding, or thermal cutting with cadmium alloys presents a significant hazard regardless of the TWA concentration, and such operations should be performed only in accordance with the recommended standard. Similarly, food storage, handling, and eating should be prohibited in cadmium work areas regardless of TWA concentrations.

VI. WORK PRACTICES

Chapter III discussed the acute toxicity of cadmium oxide fume at high concentrations, sometimes causing fatal pulmonary edema. Overexposures to freshly formed cadmium fume can develop especially from three types of processes:

Burning or welding of cadmium-plated metals.

Silver brazing with cadmium-containing alloys, rods, solders, or wires.

Heating or burning of other cadmium-containing substances.

These procedures involve temperatures ranging from above that of cadmium's melting point (321 C, 610 F) to beyond its boiling point (765 C, 1409 F). The closer the temperature to the boiling point of cadmium the more freely and profusely its fresh fume is evolved into the worker's breathing zone to cause a great risk of overexposure with acute poisoning. (Cadmium metal vapor or fume would be expected to oxidize rapidly to form cadmium oxide fume.)

(a) Recognition

Even at lethal concentrations, cadmium fume or dust has no specific warning odor or immediately irritating effects, so far as is known. Thus, any operation involving cadmium-containing or cadmium-plated substance and any form of heating, such as welding, brazing, soldering, or grinding, is likely to be highly hazardous. Moreover, cadmium-plated metals are often mistaken for galvanized or zinc-plated metals. Consequently, specific determination of the presence or absence of cadmium in products to be subjected to processes involving heat is essential. Chemical analyses of suspect metals should be conducted to confirm the presence or absence of cadmium. If this is not possible, a spot test can be used. One spot test that can be used with welding rods involves a very gentle heating of a small spot of metal, about the size of a nickel (be sure not to burn off the metal). After this gentle heating, cadmium will form a gold-yellow film, whereas zinc will turn a smoky-gray color. Another spot test involves the application of one drop of a 10% *fresh* solution of ammonium nitrate to the clean metal surface. Let the nitrate solution dissolve some of the metal for a few seconds. Blot the wet area with a filter or similar paper. Apply one or two drops of a 5% *fresh* solution of sodium sulfide to the wetted portion of the filter paper. If a yellow color develops on the wet paper area, the metal tested contains cadmium. If the paper remains colorless, no cadmium is present.[47]

(b) Silver Brazing

Silver brazing, commonly called silver soldering, is the process of joining metals by heat with a silver alloy filler metal. Many filler metal alloys contain cadmium, which can produce cadmium oxide aerosol when overheated, so care must be taken to control the temperature of silver brazing operations if the alloy contains cadmium. Under no circumstances should a torch flame be applied directly to such an alloy. The heat of the base metal should be used to melt the filler metal and cause it to flow. Silver brazing with cadmium-containing alloys should be performed only with satisfactory local exhaust or with appropriate respiratory protection.

(c) Welding, Cutting, and Heating

Welding and thermal cutting of material containing cadmium must be performed only with local exhaust ventilation demonstrated by sampling and analysis of breathing zone atmospheres to be sufficient to maintain airborne cadmium at or below recommended limits. For single operations, where local exhaust ventilation is not available or where air sampling and analysis has not demonstrated acceptable air concentrations, suitable respirators (listed in Chapter I) must be provided and worn.

Where molten cadmium is used or formed, temperatures should be kept as low as possible consistent with the requirements of the work operation to prevent generation of excess fume. Wherever possible, this should be accomplished by automatic controls, with recording of temperatures and use of alarms or other indicators of excessive temperatures. If possible, avoid using cadmium-containing alloys for brazing. In any case, cadmiumcontaining metals must be appropriately segregated and labeled, so that workers will not unknowingly apply heat to cadmium.

(d) Engineering Controls

Control design criteria for a number of cadmium fume-generating operations are given in *Industrial Ventilation—A Manual of Recommended Practice.*[258] Local exhaust ventilation should be provided at all operations as shown in this manual. Inasmuch as cadmium is more toxic than most of the other materials handled, enclosure should be maximized and the high end of any range of control velocities should be used.

Air volumes tabulated for welding[258,260] are calculated for a control velocity of 100 feet/min. For cadmium fume, control velocities of 150 feet/min should be used, so that volumes 50% greater than the tabulated volumes should be used.

Local exhaust systems should be designed and operated in conformance with ANSI Z9.2-1971, *Fundamentals Governing the Design and Operation of Local Exhaust Systems.*[260] It should be emphasized that the aim of these control procedures is adequate performance, ie, achievement of airborne concentrations at or below environmental limits and prevention of other forms of absorption such as ingestion. Published designs for ventilation control illustrate approaches which have been successful in certain applications. Any method for meeting these recommendations consistent with the health and safety of workers may be acceptable. In each case, success of control measures must be demonstrated by appropriate air sampling.

Enclosures, exhaust hoods, and duct work must be kept in good repair so that design air flows are maintained. Air flow should be measured at each hood at least twice a year, and preferably monthly. Continuous air flow indicators are recommended, such as water or oil manometers properly mounted at the juncture of fume hood and duct throat; these should be marked to indicate acceptable air flow. A log showing design air flow and results of periodic inspection should be kept.

Effluent air should be cleaned, if necessary, to meet any emission standards that may be promulgated (there are now no EPA emissions standards for cadmium). Air from the exhaust ventilation system must not be recirculated into the workplace.

(e) Respiratory Protection

For adequate respiratory protection against the many conditions that may be encountered in individual operations, many types of respirators have been developed and approved. Each has particular applications and limitations from the standpoint of protection, and each has its advantages and disadvantages from the standpoint of operation and maintenance. Detailed information on the selection and use of respirators can be obtained from *Respiratory Protective Devices Manual.*[278] ANSI Z88.2-1969[259] also classifies, describes, and gives limitations of respirators.

Respirators fall into several classifications, according to their mode of operation: (1) atmosphere-supplying respirators, which include those to which suitable air is supplied by tanks carried by the wearer or by a hose carrying air from a remote source (self-contained masks, hose masks, airline masks, and combination self-contained and airline masks); (2) air-purifying respirators which filter or absorb the contaminant (gas mask with chemical cartridge, particulate masks, and combination masks for gas, vapor, and particulate); and (3) combination atmosphere-supplying and air-purifying respirators. The factors that affect the overall performance of air-purifying respirators are the reliability of the face seal, the efficiency of the filters, and other variables such as leakage from exhalation valves.

The applicable regulation on certification and approval of respirators is 29 CFR 11. This requires, among other things, that all air-purifying respirators approved for dusts and fumes with an environmental limit less than 0.05 mg/cu m be equipped with a high efficiency filter.

(f) Protective Clothing

Protective clothing is not normally required for cadmium operations. It is possible that cadmium dust collected on clothing could be released into the air to cause a secondary exposure so that, if such clothing were worn to the worker's home, the worker and others might be exposed to cadmium

dust. The better solution is to improve workplace housekeeping to prevent clothing contamination, but it seems a wise precaution that work clothing be changed at the end of the workshift and not carried home. Thus, there should be change rooms with separate storage areas, such as lockers, and shower and hand washing facilities should be provided.

(g) General Housekeeping

Where cadmium-containing dust may exist, cleaning should be performed by vacuum pickup or wet mopping to minimize generation of airborne dust; no dry sweeping or blowing should be permitted. Prompt cleanup of spills, repair of equipment and leaks, proper storage of materials, and collection of cadmium-containing dust must be emphasized to workers and supervisors.

(h) Personal hygiene

Cadmium is toxic by ingestion, so sanitary provisions to prevent food contamination are essential. As a minimum, such precautions should include the prohibition of eating, food handling, or food storage in the workplace areas where cadmium contamination can occur. Hands should be washed before eating or before using tobacco products. Smoking in the work area can increase exposure by contamination of the smoking materials, so smoking or carrying of tobacco or tobacco products open to the air should be prohibited.

While there isn't good reason to believe that cadmium compounds penetrate the skin to a significant extent, it is good practice to avoid skin contact and if contact has occurred to wash the affected areas promptly.

(i) Storage

Cadmium-containing, including cadmium-plated, metal parts should be kept separate from parts not containing cadmium so that accidental exposures resulting from welding and cutting will not occur.

(j) Emergency Procedures

Emergency procedures should be established for any event that might result in substantial release of airborne cadmium. Such procedures should include provisions to notify the attending physician that exposure to high concentrations of cadmium fume may cause lung edema. This edema may not become evident until 8-24 hours after the exposure.

Emergency procedures should also include provision for appropriate respirators specified in Chapter I.

It is important to design specific emergency procedures to be followed in the event of a fire, to protect both workers and firefighters.

VII. COMPATIBILITY WITH OTHER STANDARDS

The Environmental Protection Agency has not classified cadmium as a hazardous pollutant and neither emission nor ambient air standards have been issued.

EPA has not promulgated solid waste regulations for cadmium. However, it has reaffirmed the 1962 PHS drinking water standard of 0.01 mg/liter[279] as an interim primary drinking water regulation, applicable to community water supplies (*Federal Register* 40:59570, December 24, 1975). While this standard is for community water supplies, and thus is not directly applicable to discharge of cadmium into streams, it seems clear that disposal of cadmium waste, liquid or solid, should be in a manner not leading to its introduction into drinking water.

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IX. APPENDIX I

AIR SAMPLING METHOD

Apparatus

(a) A cellulose ester membrane filter of nominal pore size 0.8 μm is recommended.

(b) The filter should be mounted in a holder with a cover to protect it during sampling. One or more holes of approximately 4 mm in diameter must be provided in the cover for airflow during sampling (eg, a Millipore Field Monitor in which the inlet plug has been removed).

(c) Connections between the filter holder and the sampling pump must be made in a manner to prevent leakage.

(d) The air sampling pump must be equipped with a means of indicating flow, either directly by a rotameter or indirectly by a suitably geared motor revolution counter.

(e) The air sampling pump should be calibrated so that flow may be determined to within 5%. A spirometer, wet-test meter, bubble meter, or the equivalent, can be used for calibration (see discussion of calibration). A rotameter may be used as flow indicator but should not be used for calibration of pumps with pulsating flow.

(f) Battery-operated pumps must be capable of at least 4 and preferably 8 hours of continuous operation without recharging.

Sampling Procedure for Determining Worker Exposure

(a) Samples should be taken within 50 cm of the worker's nose and mouth.

(b) Each sample for TWA concentration estimation should be taken for 2 or more hours and combined to obtain a TWA concentration for an entire shift. The most meaningful results will be obtained by combining four 2-hour samples (for an 8-hour shift). A single full-shift sample (8-10 hours), two 4-hour samples, or other combinations of full-shift consecutive samples, are also acceptable.

(c) Partial-period consecutive or intermittent samples, for example a number of 15-minute samples for estimation of TWA and ceiling concentrations, are acceptable if they adequately represent full-shift exposure.

(d) Air samples for TWA determinations should have sample volumes of at least 50 liters. A sampling rate of 1.0-2.0 liter/min for personal samples is recommended. Personal samples may be taken at rates of 0.5-3.0 liters/min.

(e) For each air sample, there should be a record of: the date, time, and place of sampling; the operation(s) being carried out during the sampling; the device used to obtain the sample; the sampling rate and sampling period; the name of the person collecting the sample; and other relevant information. Each sample must be clearly labeled for identification.

Sampling Procedure for Determining Control Effectiveness or Need for Personal Protection

(a) Area samples may be taken with the apparatus used for determining worker exposure, or with electrostatic precipitators.

(b) The sample should be taken at a site representative of the area being contaminated. The site should be identified for future sampling.

Calibration of Sampling Trains

The accurate calibration of a sampling pump is essential for the correct interpretation of the volume indicator. The necessary frequency of calibration is dependent on the use, care, and handling to which the pump has been subjected. In addition to the normally scheduled calibration, pumps should be recalibrated if they have been subjected to misuse, just received from a manufac-

turer, or just repaired. If the pump receives hard usage, more frequent calibration may be necessary.

Ordinarily, pumps should be calibrated in the laboratory before they are used in the field and at frequent intervals if they are used to collect numerous field samples. The accuracy of calibration is dependent on the type of calibrating instrument used as a reference. The choice of calibrating instrument may depend largely upon where the calibration is to be performed. For laboratory testing, a 1- or 2-liter buret or a wet-test meter is recommended, although other standard calibrating instruments, such as a spirometer, Marriott's bottle, or dry-gas meter, can be used.

Instructions for calibration with the soapbubble flowmeter follow. However, if an alternative calibration device is selected, equivalent procedures should be used. The calibration setup for personal sampling pumps with a cellulose filter is shown in Figure XIV-1. Since the flowrate indicated by the flowmeter of the pump is dependent on the pressure drop across the sampling device, a membrane filter with appropriate backup pad, the pump flowmeter must be calibrated while operating with a representative filter and backup pad in the line.

(1) While the pump is running, the voltage of the pump battery is measured with a voltmeter to assure that the battery is charged adequately for calibration.

(2) Place the cellulose membrane filter with backup pad in the filter cassette.

(3) The calibration setup is assembled as shown in Figure XIV-1.

(4) The pump is turned on and the inside of the soapbubble meter is moistened by immersing the buret in the soap solution and drawing bubbles up the tube until they are able to travel the entire length of the buret without bursting.

(5) The pump is adjusted to provide a flowrate of 2.0 liters/min.

(6) The water manometer is checked to ensure that the pressure drop across the sampling train does not exceed 13 conventional inches of water (3.23 kPa) at 2 liters/min.

(7) A soapbubble is started up the buret and the time it takes the bubble to travel a minimum of 1.0 liter is measured with a stopwatch.

(8) The procedure in (7) above is repeated at least three times, the results are averaged, and the flowrate is calculated by dividing the volume between the preselected marks by the time required for the soapbubble to travel the distance.

(9) Data recorded for the calibration should include the volume of air measured, elapsed time, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

X. APPENDIX II

ENVIRONMENTAL ANALYSIS

Determination of Cadmium in Air Samples by Atomic Absorption Spectroscopy

(a) Principle of the Method

Airborne cadmium dust and fume samples are collected on cellulose ester membrane filters or other collection systems as described in Appendix I. The filter samples are wet-ashed, using nitric acid. Analysis is performed by aspiration of the ashed sample solution into the flame of an atomic absorption spectrophotometer, and comparing the instrument response to that of a standard.

(b) Range and Sensitivity

The sensitivity in conventional flame atomic absorption may be 10-25 ng Cd/ml/0.0044 absorbance units, with detection limits as low as 1 ng Cd/ml, depending on operating conditions and instrumental variations. Using a sensitivity of 20 ng Cd/ml with an air sample of 100 liters (eg, 100 minutes at 1 liter/min) and a final liquid volume of 5 ml, the sensitivity is 1 μg Cd/cu m. For these same air and liquid volumes, the linear response range extends up to 100 μg Cd/cu m (final liquid concentration of 2 μg Cd/ml). Samples may be diluted to provide cadmium concentrations in this range.

(c) Interferences, Precision, and Accuracy

Interferences with this method are not normally encountered in the analysis of air samples. The precision for spiked samples has been determined to be 4% relative standard deviation; a larger deviation could be expected for "real" samples, using a similar method.[255] The accuracy has not been determined; however, recoveries of 90% were reported, using 20 replicates.[251] Collaborative testing has not been performed. The dependability of a similar procedure has been tested[255] and is discussed in Chapter IV.

(d) Advantages and Disadvantages of the Method

Analysis can be performed quickly and accurately by a technician experienced in trace analysis. Atomic absorption instrumentation, although not available in all laboratories, is becoming increasingly popular. The speed of the analysis by this method is a distinct advantage.

(e) Reagents and Apparatus

American Chemical Society (ACS) reagent grade chemicals or materials of similar quality are required.

(1) Concentrated nitric acid: redistilled or of trace metal quality. Use in subsequent steps where nitric acid is designated.

(2) Water: double distilled or distilled deionized.

(3) Standard cadmium solution: 1000 μg/ml. Dissolve 1.000 g of metallic cadmium in nitric acid and dilute to 1 liter in a volumetric flask with sufficient water and nitric acid to yield a solution containing 10% nitric acid. This solution is commercially available.

(4) Atomic absorption apparatus with a cadmium hollow cathode lamp, readout accessory, and gas supply system. Operating conditions recommended by the manufacturer should be followed for gas flow rates and other instrumental variables. The resonance line for cadmium is 2,288 Angstroms.

(5) Hot plate, capable of 300 C.

(f) Quality Control

Establishment and maintenance of total analytical quality control systems to assure continued precision and accuracy of laboratory reports include, as appropriate, these requirements:

(1) Each test must be checked on each day of use.

(2) At least one standard (it may be an instrument standard) and one control sample (working value established and run through the entire analytical procedure) should be included with each run of unknown samples. Where the

control sample is not subject to the interferences in the unknown samples, a previously run unknown should be included as a blind check sample. A blank sample (no added amount of the constituent being determined) should also be run to aid in detecting reagent contamination and other problems important near the lower limit of operation of the method.

(3) If the results on the standard, control, blank, or recycle samples are not within acceptable limits, the entire batch of analyses must be repeated and consideration should be given to the nonacceptance of samples where there is only enough material for a single analysis. There may be situations where this policy is waived. Consideration of the consequences of reporting results when the analytical system is apparently "out of control" should minimize such waivers.

(g) Procedure

(1) Trace Analysis Precautions

All glassware should be thoroughly cleaned and rinsed. Cleaned glassware should be soaked overnight in 10% nitric acid or one-half hour in 50% nitric acid prior to use. Glassware taken from routine laboratory use should be checked for cadmium leachability before it is integrated into the trace analysis system. Note that it is sometimes the case that previous use will make glassware unsuitable for trace analysis.

Analysts are cautioned concerning the potential for contamination of samples by smoking. Hands should be washed and smoking forbidden in the trace analysis facility.

(2) Standardization

Standards are prepared from the 1,000 μg/ml standard solu- tion by serial dilution with 1% nitric acid. Because of the loss of trace metals to glassware or plastic, dilute standards should be made daily unless in-house data show no depletion when compared with fresh standards. Standards are prepared in the 0.02 to 2 μg/ml range; standards should preferably bracket the samples. Aspirate the standards into the flame and record the instrument response. Prepare a graph of the results by plotting the absorbance vs concentration for each standard. Other instrumental output, such as percent absorption, may be used over a narrow range of concentrations. Instruments with devices that read directly in terms of concentration are also suitable.

(h) Analysis of Samples

Sample, control sample (working value previously established by carrying through entire analytical procedure), and blank are placed in suitable acid-washed vessels. For personal samplers employing 37 mm or similar filters, 50-ml Griffen beakers are suitable. Next, 3 ml of concentrated nitric acid is added and the vessel is covered with a watch glass. Each sample is heated on a hot plate in an exhaust hood until the volume of nitric acid is reduced to approximately 0.5 ml and is pale yellow or water white. Further additions of nitric acid may be necessary for complete oxidation of the filter. The cooled sample is transferred to a suitable volumetric vessel, after rinsing the watch glass. A 5-ml graduated cylinder has been employed successfully. The transfer and volume adjustment are effected with 1% nitric acid solution.

The resulting blank, control and sample solutions are aspirated into the flame of the instrument and the instrument response recorded. Samples may be diluted or concentrated to correspond to the standards. If concentration is necessary, the aspiration flow rate should be checked to assure that it is comparable to those for the standards.

(i) Calculations

Absorbances of sample and blank solutions are converted to concentration values by comparison with a curve of absorbance vs concentration prepared from the standards. The blank, which represents the level of contamination in the system, is subtracted from the sample value. The concentration of cadmium in the environmental sample is determined by the following formula:

$$\mu\text{g Cd/cu m} = \frac{\text{Cd} \times \text{S}}{\text{V}}$$

where Cd = Sample concentration minus blank concentration from standard curves, in μg Cd/ml

S = Solution volume, in ml

V = Volume of air sample, in cubic meters

XI. APPENDIX III

DETERMINATION OF PROTEIN IN URINE

Urine protein concentrations can be determined by reaction with sulfosalicylic or trichloracetic acid or by reaction with phosphotungstic acid followed by biuret analysis. Conventional clinical procedures for urine protein detection, such as the boiling test, are not adequate for detection of cadmium-induced proteinuria, because most of the proteins excreted by those intoxicated by cadmium are of low molecular weight. Specific details of analysis of urine protein by the methods mentioned above are described in the following discussion. In addition, some comments on more specific examination of urine proteins by electrophoresis or by β_2-microglobulin analysis are offered.

While 12-hour or, preferably, 24-hour urine samples are superior to spot samples, spot samples will often be all that can be obtained. Early morning samples are preferred if only spot samples can be obtained. If these samples have a low specific gravity (eg, below 1.01), further samples should be taken. For further treatment of data from urine analysis, correction for the dilution of the urine should be made. This is usually performed by correcting to a standard specific gravity, eg, 1.024, or by dividing the amount of urine protein in the sample by the amount of creatinine in the same sample.

Piscator (written communication, May 1976) has compared the methods of protein determination described below, and concluded that neither trichloroacetic acid nor sulfosalicylic acid is so useful for quantitative protein determination as the phosphotungstic acid-biuret method. With sulfosalicylic acid, an acceptable standard curve was obtained, but with trichloroacetic acid he was not able to obtain an acceptable standard curve at low protein concentrations. With sulfosalicylic acid, he found in two cases average urine protein concentrations of about 50-60% of the values obtained on the same urines with phosphotungstic acid-biuret analysis. On this basis, he suggested that while sulfosalicylic acid analysis might be useful for routine checking of urines of workers, more quantitative examinations should be performed at intervals of 1-2 years. He pointed out that even the best quantitative methods for total protein might fail to detect the first changes of tubular proteinuria, citing a case whose protein excretion was at the upper normal level but who had, on electrophoretic examination of urine protein, a pattern typical of tubular proteinuria and a significant increase in excretion of β_2-microglobulin.

Sulfosalicylic or Trichloroacetic Acid Analysis

For analysis of urine protein by precipitation with sulfosalicylic or trichoroacetic acid, the methods described by Henry et al[280] and Meulemans[281] can be used. Measure the specific gravity and the volume of the urine sample, and, after gentle mixing, filter about 75 ml; the sample should be at room temperature. Check for the approximate concentration of protein by some procedure such as use of Albustix® If the estimated concentration is higher than 150 mg/100 ml, dilute the sample with saline solution (0.99%) to a protein concentration of about 100 mg/100 ml.

Pipet 0.5 ml of urine into each of 2 tubes. Add to the first tube 2 ml of saline solution and to the other 2 ml of 3% sulfosalicylic acid or trichloracetic acid. Mix the contents of each tube immediately after the addition and let stand for 5 minutes, followed by a second mixing and reading of the absorbance in a spectrophotometer at 620 nm against a reagent blank. Subtract the reading of the reagent blank and the reading of the urine sample to which saline was added from the reading of the reagent-treated urine sample. Calculate the

total amount of protein (per unit of volume or per unit of time such as 12 or 24 hours) from the standard curve. According to McGarry et al, [282] normal urine protein excretion is about 70 mg/day but may be as high as 90 mg/day; these values are equivalent to 5 and 6.4 mg/100 ml if daily urine excretion is about 1,400 ml. It is likely that better estimates of normal urine excretion of protein can be developed from analyses of urine samples taken at preplacement examinations of workers.

For preparation of a standard curve, use a serum sample with a known protein content and dilute 3:100 with saline solution. Prepare standards by diluting 1, 2, 4, 6, 8, and 10 ml of diluted serum with saline to 10 ml. As with the urine samples, pipet 0.5 ml of each dilution into each of two tubes, add 2 ml of saline to one and 2 ml of sulfosalicylic or trichloroacetic acid solution to the other, mix and let stand for 5 minutes, then mix again and read absorbance at 620 nm, subtracting the absorbance of the reagent blank and that of the serum plus saline from the absorbance of the reagent-treated serum. Plot the resultant absorbances against the protein concentration to get the standard curve. If, for example, the protein concentration of the serum were 7.2 g/100 ml, the diluted standard samples would be 0.22, 0.43, 0.86, 1.30, 1.73, and 2.16 g/liter.

Phosphotungstic Acid-Biuret Analysis

At the Department of Environmental Hygiene, Karolinska Institute, a method of analysis of urine protein has been used for many years that involves precipitation of urine protein by Tsuchiya's reagent, followed by biuret analysis. This method appears to be better than analysis by sulfosalicylic acid or trichloracetic acid in that it can detect urine protein more sensitively than is possible by the other methods. The methods involving reaction with sulfosalicylic or trichloracetic acid have the advantage of involving procedures more familiar to many clinical laboratories.

The procedure as described by Piscator[283] involves mixing 1-2 ml of urine with an equal volume of Tsuchiya's reagent. This reagent is made from 15 g of phosphotungstic acid, 60 g of concentrated hydrochloric acid, 770 ml of 95% ethyl alcohol, and 60 ml of distilled water. After 15 minutes, the precipitate formed by reaction of urine protein with Tsuchiya's reagent is centrifuged at 3,500 rpm. It is then washed twice with 95% ethyl alcohol and dissolved in 4 ml of 3% sodium hydroxide, followed by the addition of 0.2 ml of Benedict's reagent. The Benedict's reagent is made by dissolving 173 g of pure sodium citrate and 100 g of dry sodium carbonate in 500-600 ml of distilled water with the aid of gentle heating, but avoiding boiling. While still warm, the solution is filtered. Meanwhile, 17.3 g of copper sulfate pentahydrate is dissolved with heating in about 100 ml of distilled water. The two solutions are then mixed and after cooling made up to 1,000 ml with distilled water. This mixture is kept in dark bottles with rubber stoppers.

With human albumin as the standard, as described by Piscator,[283] and sample cells of 1 cm light path, readings of the biuret color are made in a spectrophotometer at 330 nm, comparing the readings with those from a blank consisting of 4 ml of 3% sodium hydroxide and 0.2 ml of the Benedict's solution.

Piscator[283] found that when trichloroacetic acid was used as the precipitating agent, much lower values were obtained than with Tsuchiya's reagent when the centrifuge rate was 3,500 rpm. But at a centrifuge rate of 10,000 rpm and a final trichloroacetic acid concentration of 4%, values obtained were similar to those obtained with Tsuchiya's reagent.

Examination for Tubular Proteins

There are probably many individual proteins in normal urine as well as in urines of workers with abnormal proteinuria from cadmium intoxication. Electrophoretic patterns of urine proteins presented in a review by Piscator[284] show lower albumin content in cadmium workers than in the normal man, but a higher content of some fractions that correspond with some of those found in serum. The electrophoretic patterns of the urines of the cadmium workers were characterized by peaks corresponding to α_2-, β-, and γ-globulins, with the elevation due to the β-fraction being especially marked. This β-globulin peak is accounted for by a microglobulin named by Berggard and Bearn[69] as β_2-microglobulin, which they isolated from the urines of patients with chronic cadmium poisoning and of patients with Wilson's disease, which is also a disease involving tubular proteinuria.

Enzymes such as muramidase and ribonuclease have also been found in the urines of people occupationally exposed to cadmium[74,284]

Radioimmunoassay and single radial immunodiffusion have been used for β_2-microglobulin assay, and values obtained by these methods correlated well, according to Evrin et al.[275] They found the average concentration of this protein in urines of 10 healthy subjects to be 73 μg/24-hour volume, by radioimmunoassay. In another study by these University of Uppsala investigators, Peterson et al[285] found the average 24-hour excretion of this microglobulin in healthy subjects was 120 μg. Average 24-hour albumin excretion in these subjects was 10 mg and total protein 80 mg. Patients with glomerular disorders had normal or only slightly increased excretion of microglobulin but marked increases in albumin and total protein excretion. Most of the patients with tubular disorders had large amounts of microglobulin in their urines with normal or only slightly increased quantities of albumin and only moderately increased quantities of total protein. These investigators[285] used the single radial immunodiffusion method of Mancini et al[286] for determination of albumin and microglobulin in urine. Sevier and Reisfeld[276] have described a semi-automatic method for double-antibody radioimmunoassay capable of analyzing 24 samples simultaneously in the range of 1-100 ng, using goat anti-β_2-microglobulin and Sepharose-bound rabbit anti-goat-immunoglobulin G. Facilities for microglobulin analysis are not available in many laboratories.

Evrin and Wibell[287] reported that β_2-microglobulin can decompose during storage of urine samples with pH of less than 5.6. This can be prevented by adding buffer to urine samples. However, Kjellstrom et al[132] suggested that this decomposition might also occur in the urinary bladder if the urine pH were below 5.6. They found an average of 450 μg/liter in 15 urine samples of pH less than 5.6 and an average of 2 mg/liter in other samples of higher pH.

XII. APPENDIX IV

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, *An Identification System for Occupationally Hazardous Materials.* The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, ie, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or if not available, from other sources of publications, such as the American Conference of Governmental Industrial Hygienists of the American National Standards Institute Inc. Flammability or reactivity data could be flash point, shock sensitivity, or other brief data indicating nature of the hazard.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in millimeters of mercury (mm Hg); vapor density of gas or vapor (air + 1); solubility in water, in parts/hundred

parts of water by weight; specific gravity (water + 1); percent volatiles (indicated if by weight or volume) at 70 Fahrenheit (21.1 Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flash point and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a permissible exposure limit or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed workers.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect workers assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Pertinent specific local requirements shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," "Suitable for dusts not more toxic than lead," etc. Protective equipment must be specified as to type and materials of construction.

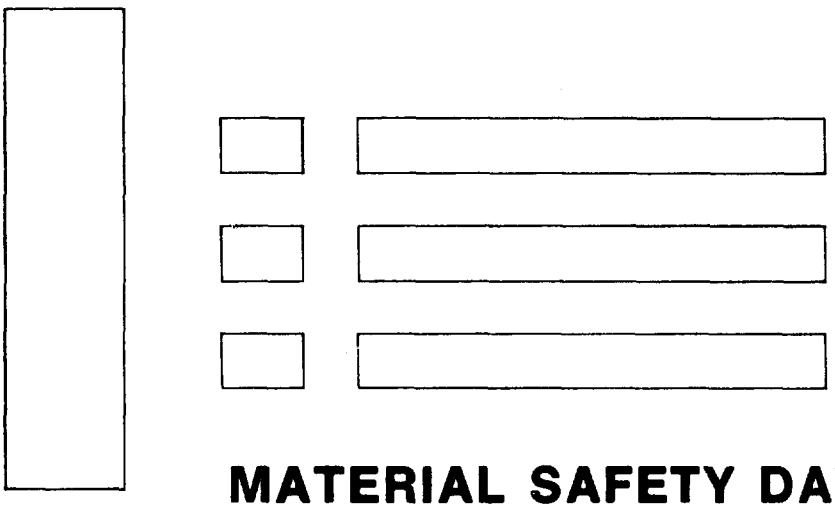
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to workers potentially exposed to the hazardous material. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL.		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN:

INHALATION:

INGESTION:

NOTES TO PHYSICIAN

VI REACTIVITY DATA
CONDITIONS CONTRIBUTING TO INSTABILITY
INCOMPATIBILITY
HAZARDOUS DECOMPOSITION PRODUCTS
CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION
VII SPILL OR LEAK PROCEDURES
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED NEUTRALIZING CHEMICALS
WASTE DISPOSAL METHOD
VIII SPECIAL PROTECTION INFORMATION
VENTILATION REQUIREMENTS
SPECIFIC PERSONAL PROTECTIVE EQUIPMENT RESPIRATORY (SPECIFY IN DETAIL)
EYE
GLOVES
OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

XIII. APPENDIX V

RESEARCH NEEDS

Various effects of cadmium have been studied in animals, but their relevance to humans at workroom concentrations is not clear, and appropriate information should be developed. One of the more important of these gaps pertains to gonadal effects. The study of such effects in cadmium workers poses problems, because of the difficulty in studying gonadal function and the impracticability of obtaining biopsies. Post-mortem examinations may be useful but will often be complicated by senile or terminal changes. The possible role of vascular changes or of alterations in zinc utilization in the gonadal effects should be investigated.

Another important area is in vascular effects of cadmium exposure, since there is conflicting information on the role of cadmium in hypertension and because of suggestions that vascular effects mediate such other effects as those on renal function.

More evidence on the role of cadmium in development of fetal abnormalities in man is needed. Additional assurance is needed that, if cadmium absorption is maintained at sufficiently low levels so that zinc availability to the fetus will not be altered, offspring of cadmium workers will not be harmed by their parents' exposure. In this connection, there is a need for a national surveillance system that can gather information on fetal deaths or anomalies and errors in development of children and relate these data to occupational exposures (or other environmental stresses) of the parents.

The present inadequacies and conflicts in information, from both human and lower animal investigations, on whether cadmium can cause mutations or cancer should be corrected. Further epidemiologic investigations in populations not exposed to other possible causes of these effects should be pursued. At the same time, life-time studies in experimental animals at appropriate doses should be performed. These doses should be high enough to cause significant toxic effects from cadmium but not so high as to cause a significant decrease in longevity, for data to be properly interpretable. Further evidence bearing on the suggestion that cadmium is involved in the causation of prostate cancer should be obtained, preferably from worker populations not also exposed to other possible carcinogens. In this connection, a mortality study now underway at the Karolinska Institute may shed further light on this question. This study of worker populations exposed to cadmium involves two cohorts, one of about 200 and the other smaller. Evaluation of the data developed may be completed within the year (L Friberg, verbal communication, June 1976).

Evidence on adverse effects of cadmium on the nervous system, on the pancreas, on the adrenals, and on thyroids and parathyroids should be confirmed by additional investigations. In particular, conflicting information on whether cadmium causes liver changes at workplace exposure concentrations should be resolved.

Further investigation is also needed on the suggestion, developed in some recent epidemiologic studies, that cadmium workers who smoke may have a greater risk of development of altered renal function.

There are indications that many of the toxic effects of cadmium, possibly all the toxic effects other than some of those on the respiratory tract, result from cadmium's antagonism of the effects of zinc. Further clarification of this and of its impact on deriving safe levels of cadmium should be pursued.

Most elements of this recommended standard were based on empirical information such as epidemiologic investigations of worker populations. A more fundamental approach, such as the

approach involving the mathematical model briefly discussed in Chapter III, *Correlation of Exposure and Effect*, may become more useful when the relevant factors are better quantitated. This model approach will probably be even more useful in a more accurate development of the human organism's ability to handle cadmium from all sources, and should be especially important to those populations exposed to large amounts of cadmium from such sources as food and water. Thus, better information is needed on the absorption of cadmium in various forms by various routes, its retention (half-life) in the body and in critical organs and tissues, its distribution within the body, and, in particular, the threshold concentrations in critical organs in acute (lungs) and chronic (renal cortex) intoxications. From such studies, a better understanding of the significance of blood and urine cadmium concentrations to estimations of amounts absorbed and of the state of health of the individual is likely to be achieved.

TABLE XIV-1

PHYSICAL PROPERTIES OF CADMIUM

Atomic number	48
Atomic weight	112.40
Outer electron configuration	4d(10) 5s(2)
Melting point	320.9 C, 609.7 F
Boiling point	765 C, 1409 F
Density	8.642 g/cc

Solubility of cadmium compounds in water (0-25 C):

Soluble at more than 100 g/100 cc
Cadmium chlorate, chloride, nitrate

Soluble at 50-90 g/100 cc
Cadmium bromide, iodide, sulfate

Soluble at 1-10 g/100 cc
Cadmium benzoate, cyanide, fluoride, lactate

Insoluble
Cadmium carbonate, hydroxide, oxide, selenide, sulfide

From the Handbook of Chemistry and Physics[10].

TABLE XIV-2

SUMMARY OF EFFECTS OF CADMIUM EXPOSURE*

Species	Route	Dose or Concentration	Exposure	Investigators' Observations	Reference Number
Humans	Inhalation	2500-2900 mg-min/cu m	Once	Fatal pulmonary edema	44, 51, 52
"	"	0.1-25 mg/cu m	Years	Rickets and dental problems in offspring of workers	95
"	"	0.1-24 mg/cu m	"	General complaints, chronaxy changes	116
"	"	0.04-19 mg/cu m	"	Slight anemia, yellow fringe on teeth	62
"	"	3-15 mg/cu m	"	Anosmia, fatigue, renal dysfunction, hepatic dysfunction, emphysema, yellow fringe on teeth	55
"	"	0.1-4 mg/cu m	"	Emphysema, proteinuria	71
"	"	0.6-2.8 mg/cu m	"	Anosmia, proteinuria	65
"	"	0.028-2.8 mg/cu m	"	"	78
"	"	0.33-1.9 mg/cu m	"	Proteinuria, aminoaciduria	75, 129
"	"	20-700 μg/cu m	Years, 1 hr/day	Proteinuria	61
"	"	60-680 μg/cu m	Years	Gastrointestinal and respiratory symptoms, carious teeth	81
"	"	80-450 μg/cu m	"	Emphysema, proteinuria	59
"	"	74-210 μg/cu m	"	Reduced pulmonary function, proteinuria	135
"	"	134 μg/cu m	1-20 years	Proteinuria	133
"	"	125 μg/cu m	Years	Anemia, proteinuria	63
"	"	Below 100 μg/cu m	"	Questionable effects	131
"	"	Below 90 μg/cu m	"	Reduced pulmonary function, proteinuria	134
"	"	66 μg/cu m	21-40 years	"	133
"	"	31 μg/cu m	1-12 years	No effects	133
"	"	16-29 μg/cu m	Years	Improvement in conditions of workers exposed at 125 μg/cu m, no effects in new workers	130
Rats	po, water	50 ppm	3 months	Anemia	138
"	po, diet	45-135 ppm	6 months	Anemia, bleaching of incisor teeth	139
Rabbits	sc	650 μg/kg	10 weeks	Anemia, proteinuria	143
Rats, mice	po, water	5 ppm		Hypertension after 1 year	90
Rats	"	0.2-200 ppm	6-12 weeks	Vascular changes in kidneys	153
"	ip	1 mg/kg	45 days	Increased adrenal activity	154
"	sc	850 μg/kg	Once	Testicular necrosis	147
"	po, water	5 ppm	Up to 4 years	No significant increase in tumors	192
Mice	sc	630 μg/kg	Once	Fetal abnormalities	174
Hamsters	iv	880 μg/kg	Once	"	176
Rats	ip	1.8 mg/kg	Once	"	172
"	Inhalation	2.8 mg/cu m	7 months	Altered estrus, decreased weights of offspring	95

*Some investigators noted deaths of cadmium workers from various causes, including cancer, without necessarily attributing them to exposure. See Table III-2 for a summary of two studies that compared observed and expected deaths from cancer.

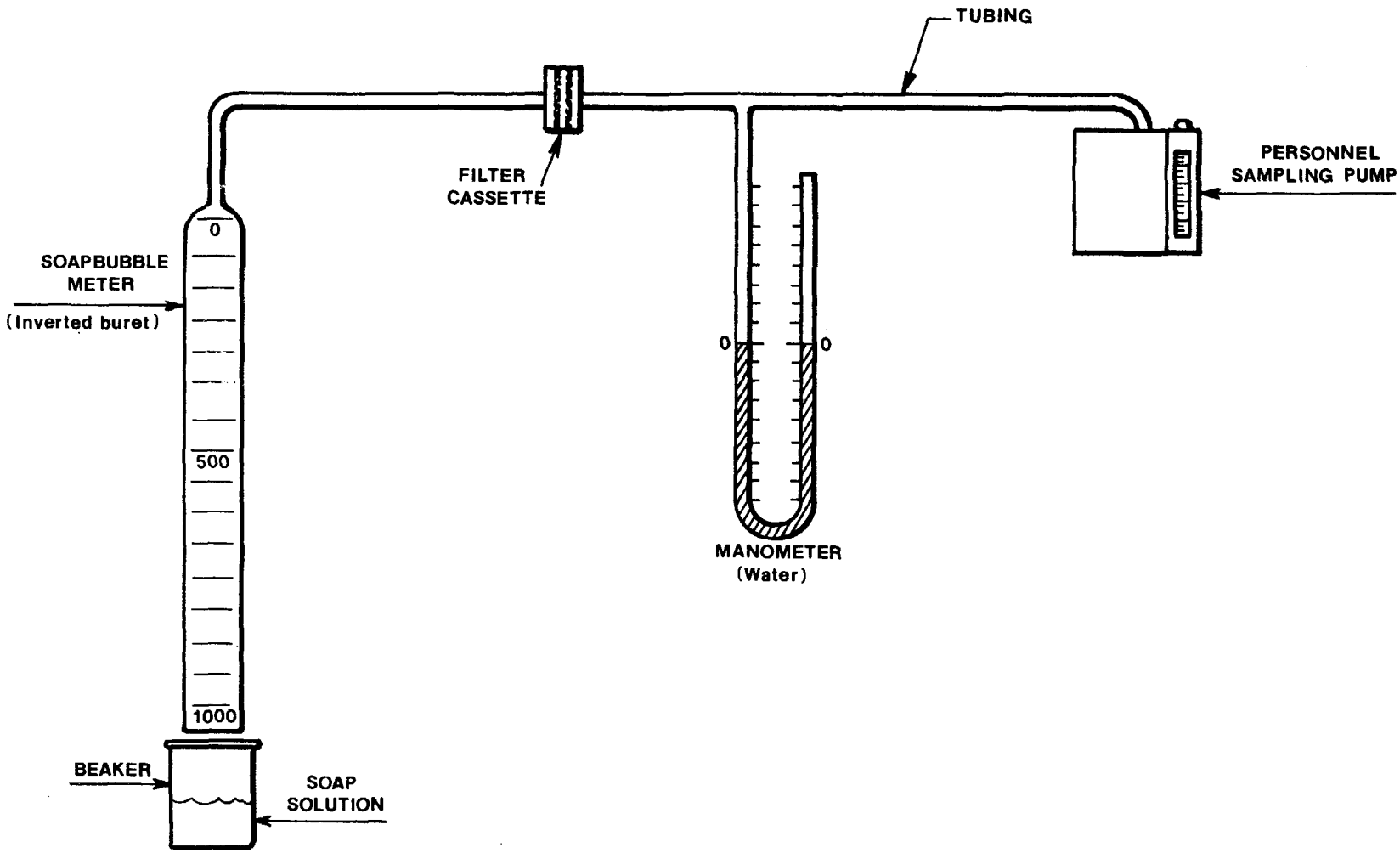


FIGURE XIV-1. CALIBRATION SETUP FOR PERSONAL SAMPLING WITH FILTER CASSETTE

*USGPO: 1977 — 757-009/212

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