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Human health effects of exposure to cadmium

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Summary. The health effects of human exposure to cadmium are discussed with emphases on intake, absorption, body burden, and excretion; osteomalacia in Japan; hypertension; and proteinuria, emphysema, osteomalacia, and cancer in workers. Elevated blood pressure has not been observed as a result of excessive exposures to cadmium in Japan or the workplace. Renal tubular dysfunction and consequent proteinuria is generally accepted as the main effect following long-term, low-level exposure to cadmium. Studies of workers show that proteinuria may develop after the first year of exposure or many years after the last exposure. Proteinuria and deterioration of renal function may continue even after cessation of exposure. The immediate health significance of low-level proteinuria is still under debate. However, there is evidence that long-term renal tubular dysfunction may lead to abnormalities of calcium metabolism and osteomalacia. The few autopsy and cross-sectional studies of workers do not permit conclusions to be drawn regarding the relationship between cadmium exposure and emphysema. Retrospective and historical-prospective studies are needed to settle this important question. No conclusive evidence has been published regarding cadmium-induced cancer in humans. However, there is sufficient evidence to regard cadmium as a suspect renal and prostate carcinogen. Because of equivocal results and the absence of dose-response relationships, the studies reviewed should be used with caution in making regulatory decisions and low-dose risk assessments.

Introduction

The main goal of this critical review was to summarize and evaluate studies of humans which could be useful in assessing the possible health effects of cadmium exposures via air, water, or food. In particular, data were sought which would permit the extrapolation of high dose effects to low levels of exposure. As indicated in the summary, the extrapolation objective was not achieved using the human literature. Whenever there were inconsistencies between the animal and limited human health effects literatures, human data were given precedence in this review.

Intake, absorption, body burden, excretion

The main routes of cadmium intake in man are the lungs and the gastrointestinal tract. The chemical form of ambient airborne cadmium is not known. Although measurements of airborne cadmium concentrations have been made in many countries, the concentrations are not strictly comparable because of different sampling times and different analytical methods. Size distributions of particles containing cadmium are rarely determined. Hence, only rough estimates of lung deposition rates can be made[14].

On the basis of limited cadmium-containing particle size distribution data and the application of a standard lung model, about 25% of cadmium inhaled in ambient air would be deposited in the lower respiratory tract[14]. Using this deposition fraction and an assumed average daily inhalation of 20 m^3, the amount of cadmium deposited in the lower respiratory tract has been estimated: rural areas, 0.0005–0.215 μg/day; urban areas, 0.01–3.5 μg/day; industrialized areas with cadmium emissions, 0.05–25 μg/day. The highest level of 25 μg/day is probably found only in the vicinity of an operation such as a smelter[14].
The rate of absorption through the lungs is a function of the chemical form and size distribution of the inhaled particles. Various rates have been reported. One model based on human smokers predicts 50% of inhaled cadmium from tobacco smoke is absorbed[17]. One pack of 20 cigarettes can contain 30 μg of cadmium of which 2–4 μg can be inhaled[17,18,21]. In the general environment 13–19% of the cadmium inhaled is absorbed[14].
Ingestion of cadmium occurs via water and food. Tap water which is not particularly contaminated contains < 2 μg/l cadmium. This corresponds to an intake of 2–4 μg/day.

Analyses of the diets characteristic of several countries show that adult cadmium intake from food ranges from 4 to 84 μg/day[14]. Dietary data from Japan are excluded as they constitute a special case where the daily intake of cadmium via food in the endemic area was calculated at 600 μg by assuming an average cadmium concentration in rice of 1 μg/g and a cadmium concentration in other foodstuffs of about 10 times the value for Japan as a whole[21]. Total daily intake from all sources can range from 6 μg for a non-smoker living in a rural area and eating less contaminated food (0.0005 μg from air, 4 μg from food, 2 μg from water) to 115 μg for a 20-cigarette/day smoker living close to a cadmium emitting source and eating more contaminated food (25 μg from air, 84 μg from food, 2 μg from water, 4 μg from cigarettes). The human gastrointestinal absorption rate ranges between 4.7 and 7% and was estimated through experiments on 5 human volunteers (19–50 years old) who were given labeled cadmium orally[14]. Animal studies[14] indicate that diets low in calcium, iron, and protein can stimulate cadmium absorption by a factor of about 2. Also, one study has shown that the rate of gastrointestinal absorption of cadmium is higher in young mice than in adults[14].

Body burden of cadmium ranges from < 1 μg in the human newborn (indicating that the placenta is an effective barrier to cadmium) to 15–30 mg in the normal adult[21]. The placenta is less permeable to cadmium than to lead and mercury. Cadmium is about 50% lower in newborn vs maternal blood[31]. For the normal adult, about 50% of the body burden is in liver and kidneys and about one-third in the kidneys alone. Kidney cortex concentrations are generally higher than kidney medulla concentrations by a factor of 1.1–9.6[21]. In normal persons, the highest concentration of cadmium is found in the kidney, followed by the liver and other organs. For a recent high-level industrial exposure, the liver will contain a higher proportion of the total body burden than the kidney. In some cases the concentration of cadmium in the liver has exceeded the kidney level[7,21,56]. The pancreas may also contain high concentrations of cadmium[21]. Accumulation in the kidneys peaks at about age 50 when mean renal cortex concentrations range between 11 and 50 μg/g wet weight[17,21]. After about age 50, cortex levels decrease[17]. The report by Elinder et al.[17] is particularly useful in that kidney cortex, liver, and pancreas cadmium concentrations are presented as a function of age. Renal cortex levels of 300 μg/g wet weight have been found in exposed workers. However, normal values have been reported despite signs of cadmium toxicity. It is thought that unexpectedly low values are due to cadmium losses following renal dysfunction. Renal damage may occur at cadmium concentrations over 200 μg/g wet weight of kidney cortex[21].

Several studies have demonstrated significantly higher kidney, liver, and lung cadmium levels in smokers vs non-smokers[17,37,38,42,55,59]. The accumulation in smokers is related to the number of pack-years smoked[38]. These studies indicate that cigarettes are a major source of cadmium and can double a smoker's vs non-smoker's kidney burden of cadmium[17,37,42].

For a non-smoker, the biological half-life of cadmium in the kidney cortex is estimated at 30 years, with an average concentration at age 50 of 11 μg/g wet weight[17]. Smokers have an average cadmium concentration in the kidney cortex of 22 μg/g wet weight at age 50[17].

Given that there are analytical problems in the analysis of blood for cadmium, there appears to be no relation between blood levels of cadmium and body burden or kidney burden[14,21]. In recently exposed workers, cadmium in blood may increase without a corresponding change in urinary cadmium output. Cadmium in blood is probably a reflection of current exposure and not body burden[14]. After cessation of exposure, blood levels decrease slowly. However, for a short, high level exposure, the initial decrease of blood cadmium may be rapid after exposure ceases[21]. Normal concentrations of cadmium in blood are < 1 μg/100 ml whole blood[14,21]. Exposed workers' blood cadmium may range between 1 and 10 μg/100 ml whole blood[21].

Normal urinary levels of cadmium increase with age and are < 2 μg/day. This increase is probably a function of the increase in kidney burden with age. Urinary cadmium is a poor index of body burden or kidney burden. The urinary level of cadmium may remain within normal limits for some time during occupational exposure. If renal tubular dysfunction occurs (signaled by an increase in excretion of low molecular weight proteins) there will be an increase in cadmium excretion which can be dramatic. Urinary excretion in exposed workers can be several hundred μg/day[14,21].

Except for the period right after exposure, fecal excretion is low. Insignificant amounts may be excreted via hair, sweat, breast milk, and saliva[21].

Metallothionein, a low molecular weight (10,000–12,000) metal binding protein rich in cysteine residues, binds with cadmium, zinc, copper, mercury, silver, and tin in vivo. It has been detected in human kidney, liver, heart, brain, testis, and skin epithelial cells. Most of the cadmium in tissues is probably bound to metallothionein[14]. Cadmium and zinc appear to be the only metals which can induce the synthesis of this protein[15,62]. Induction of metallothionein synthesis has been shown in kidney, liver, and intestine[14]. The role of metallothionein in cadmium absorption, transport, storage, and excretion is not well defined in humans. It is especially unclear whether metallothionein plays an overall protective or toxic role.

Association with osteomalacia in Japan (reference 21 unless otherwise indicated)

In 1946 'Itai-Itai byo' or ouch-ouch disease was recognized in Toyama Prefecture, Japan. In 1948 osteomalacia was suspected as the cause. Osteomalcia results from: vitamin D deficiency; malabsorption of vitamin D and bone minerals; or renal tubular dysfunction which results in loss of bone minerals

through the kidneys. The last type is called vitamin D-resistant or renal osteomalacia, and Itai-Itai disease is classified as a vitamin D-resistant form of osteomalacia. However, since most of the Itai-Itai patients were postmenopausal women who had an average of 6 deliveries, it is believed that a low vitamin and calcium intake, a high demand for calcium and vitamin D during pregnancy and lactation, and deprivation of UV irradiation were contributing etiological factors. The disease is characterized by: skeletal deformities with a marked decrease in height; lumbar pains; leg muscle pain;pain induced by pressure on bones, especially the femurs, backbone, and ribs; ducklike gait; bones susceptible to multiple fractures after very slight trauma such as coughing; impaired pancreatic function; changes in the gastrointestinal tract; hypochromic anemia; renal tubular dysfunction resulting in proteinuria[54] (low molecular weight proteins such as immune globulins and β_2-microglobulin), glucosuria, and aminoaciduria; low levels of serum iron, calcium, and inorganic phosphorous, and high levels of alkaline phosphatase.

It has been well established that excessive exposure to cadmium can result in renal tubular dysfunction with characteristic proteinuria, aminoaciduria, and glucosuria. Kidney damage seen in Itai-Itai disease has been very similar to that seen in industrial chronic cadmium poisoning[1,5,7,19-21,25,32,47,49,56,58]. Hypercalciuria also occurs as a result of renal tubular damage[25]. However, urinary calcium levels were normal in Itai-Itai patients. This may not seem so surprising if it is assumed that by the time symptoms developed, mobilization and excretion of bone calcium had already occurred.

The most probable source of excessive cadmium intake in the endemic area (Toyama Prefecture) was rice which had been grown in irrigation water contaminated with the effluents of a mining operation. The cadmium content of rice in some areas was more than 10 times the average in Japan.

Association with hypertension

Rat studies clearly indicate that cadmium administered in drinking water at levels in the range of 0.1–20 ppm can produce elevated systolic and diastolic blood pressures and increase mortality[11,29,41,44-46,51,53]. Water concentrations above this range are toxic or decrease blood pressure[29,44,45], while those below seem to have no effect on blood pressure[29,45]. Also rat studies have shown that the blood pressure elevating effect of cadmium can be inhibited by adding selenium (3.6 ppm), zinc (200 ppm), or copper to drinking water or by dissolving the cadmium in hard water rather than deinozed water[45,46]. Rat studies have also shown that there can be a genetic predisposition to the pressor effects of cadmium[41].

In spite of the rather convincing animal data, there is no direct proof of a causal relationship between cadmium and the development of human essential hypertension. Cadmium was first suspected in the early 1950's when effective antihypertensive drugs first became available. The ability to bind transition and related trace metals was a common characteristic of several of these drugs[43]. Experiments with ethylenediamine tetraacetate (EDTA) indicated that cadmium, copper, or zinc could be the metal on which these drugs acted[43]. Of these three, cadmium was most suspect due to its affinity for the kidney, an organ recognized for its critical role in controlling blood pressure. Indeed several studies have shown that humans who have died from hypertensive complications had increased renal cadmium concentrations[14,35,43,52].

However, the results of other human autopsy studies have not shown a significant correlation between renal cadmium accumulation and hypertension[14,42,48,59]. This discrepancy may be a result of uncontrolled differences between test and control groups, e.g. smoking habits, age, nutritional status, and stage of disease. Also there are possible errors due to wrong diagnosis and small sample sizes. Smoking is correlated with elevated renal cadmium. It is likely that the possible association between hypertension and elevated renal cadmium is secondary to a primary association between hypertension and smoking. Also it is extremely important to match autopsy samples not only on the basis of smoking history but also by age. This is necessary due to the 'natural' accumulation of cadmium in the kidneys of non-occupationally exposed people. However, the affect of age may be small since the majority of cadmium accumulates before age 30[52]. Stage of hypertension is important. Patients dying of malignant hypertension with renal failure have low values of renal cadmium[21,43,52]. Low renal cadmium concentrations due to severe renal damage have also been observed in cadmium-exposed workers and Itai-Itai disease[21,43]. Regarding nutritional status, a recent study[40] was designed to compare the calcium intake in humans with established hypertension to that of a normotensive group matched for age, sex, and race. Compared to 44 normotensive controls, 46 hypertensives reported significantly less daily calcium ingestion (688 ± 55 mg compared to 886 ± 89 mg). The intake of other nutrients, including sodium and potassium, was very similar in the two groups.

An important question arises at this point: if hypertension can be induced in rats at low ingested doses of cadmium, what has been the experience of people living in the cadmium-polluted areas of Japan and those occupationally exposed to cadmium? From animal experiments it is clear that high doses of cadmium do not produce hypertension. Therefore, it is not totally unexpected that the incidence of hypertension is not increased among Japanese suffering from Itai-Itai and presumably exposed to very high levels of cadmium[14,21]. What is surprising is that other Japanese living in the cadmium-polluted areas and not suffering from Itai-Itai did not develop hypertension even though some moderate level of excessive cadmium exposure was almost certain[21,43]. Also, an abnormally high incidence of hypertension has not been observed in workers exposed to cadmium dusts and fumes[1,2,5,7,9,10,14,19-25,32,33,47,49,50,52,56-58,61].

Occupational exposure

One of the earliest reports of industrial cadmium poisoning was published in 1938[13]. This report concentrated on a presentation of the acute responses of 15 workers exposed to high but unspecified levels of cadmium fumes from an annealing furnace. The first symptom was usually throat irritation occurring at the time of exposure. This irritation was not sufficient to compel the workers to leave the exposure even when fatal concentrations were being breathed. Delayed (hours or days) symptoms included chest soreness aggravated by deep breathing, dyspnea, violent coughing, nausea, vomiting, cyanosis, pulmonary edema, elevated temperature (up to 38.9 °C) and elevated pulse. Two deaths occurred after 4 and 8 days. The most distressing symptom was severe attacks of dyspnea which commenced hours or even days after exposure. Due to the delayed appearance of serious symptoms, it is possible to mistake cadmium fume poisoning for some other illness such as influenza. Also, the clinical picture of cadmium poisoning is similar to that caused by nitrous or zinc fumes[6,13]. Both cause severe lung damage which usually manifests itself hours after exposure. No permanent ill effects (such as fibrosis) were observed in the non-fatal cases during the 8-month follow-up period. An attempt was made to quantify the exposure from the annealing furnace[3]. It was concluded that a lethal exposure of thermally generated cadmium oxide, for man doing light work, is less than 2900 min-mg/m^3. Exposures less than this caused incapacitation of all men exposed. A later study in 1966 reported a similar time-concentration of 2589 min-mg/m^3 (8.6 mg/m^3 for 5 h) which had caused the death of a worker exposed to cadmium fume[6].

It was reported in 1940[7] that workers plating metals with cadmium by an electrolytic process had chronic rhinitis and pharyngitis, dryness and irritation of the pharynx, a burning sensation in the nose with nasal hemorrhage, and ulcers in the cartilaginous parts of the nose and the nasopharynx.

Friberg reported on a study of 58 workers employed in the manufacture of storage batteries[19,20]. Workers were exposed to both cadmium-iron dust and nickel-graphite dust. Air analyses showed 3–15 mg cadmium/m^3 and 10–150 mg nickel/m^3 of air. 95% of the cadmium-iron dust and 85% of the nickel-graphite dust particles were less than 5 µm. In the group of 43 workers with 9–34 years of exposure (average age, 44), 50% had pulmonary emphysema. No emphysema was observed in the 15 workers in the short exposure (1–4 years) group (average age, 35). However, a large number of the high-exposure workers had tuberculous lung changes. This finding clouds the interpretation of the emphysema since the tuberculosis may have preceded and caused the emphysema or exposure to the dust may have caused an increased susceptibility to tuberculosis[20]. There was no discussion of smoking habits. Emphysema will be discussed in more detail later. Two-thirds of the workers in the long-exposure group had proteinuria (20,000–30,000 molecular weight). No proteinuria was found in the low-exposure group. One-third of the long-exposure group had anosmia (absence of the sense of smell). A distinct yellow coloring of the front teeth occurred in workers in both the high- and low-exposure groups. Overall the workers complained of tiredness, shortness of breath, cough, and impaired olfactory sense. Friberg suspected that the emphysema, proteinuria, and anosmia resulted from the cadmium component of the dust rather than the nickel. However, it was emphasized that the nickel may have contributed to the emphysema and anosmia[20]. In a follow-up report in 1952, Friberg and Nystrom[7] re-examined the 43 men who had more than 9 years employment in the battery industry. There had been no further exposure to cadmium in the intervening years. Five had died: 2 due to emphysema, 2 due to coronary thrombosis (severe renal damage attributed to cadmium was found at autopsy), and 1 died from acute pancreatitis (lungs were found to be emphysematous). In 9 of the remaining 38, disease had progressed: increased dyspnea in 5, development of proteinuria in 4, deterioration of renal function in 3. The symptoms of 25 were unchanged, and in 4 there was a distinct improvement in the performance of respiratory function tests.

Proteinuria has been reported in cadmium workers many times since Friberg's report[1,5,7,14,21,25,32,47,49,56,58,61]. Exposures of 50–1000 µg cadmium dust/m^3[1], 3–67 µg total cadmium/m^3[5], 75–240 µg time-weighted cadmium fume/m^3[61], and 134 µg cadmium dust/m^3[32], have resulted in proteinuria. The minimal latent period before onset of proteinuria is about 1 year from the beginning of exposure[61]. However, the first sign of disease may develop many years after the last exposure[8]. Urinary protein increases gradually to < 110 mg/100 ml in most cases[1]. Normal adult urinary protein excretion averages 50 mg/day. Cadmium exposed individuals excrete 70–2600 mg/day[47]. Recent work indicates that the kidney lesion is first glomerular and later becomes predominantly tubular[5,32]. The sedimentation and electrophoretic properties of urine proteins from patients with known tubular dysfunction are similar to those found in cases of chronic cadmium poisoning[8,25]. Although Bonnell states that most cases of proteinuria are well compensated and symptoms of renal failure are rare[8], autopsy studies of cadmium-employed workers have shown evidence of severe renal damage[2,7].

Once established, proteinuria persists even after cessation of exposure[1]. There was no evidence in the study by Adams et al.[1] that renal function continues to deteriorate after cessation of exposure. However, others have reported that deterioration of renal function does continue after exposure ceases[7,9,10]. There has been at least 1 fatal case of chronic renal failure in a cadmium worker. The exposure was estimated at several hundred µg cadmium fume per m^3[7].

Some researchers feel that the significance of cadmium-induced proteinuria has not yet been established[8,25,49]. Others take the position that cadmium-induced proteinuria is clinically significant and should be regarded as an early manifestation of renal tubular damage[1,25].

Additional abnormalities suggestive of renal tubular

malfunction have been found in cadmium workers: glycosuria, impaired acid excretion, hyperchloremic acidosis, abnormal aminoaciduria, impaired concentrating ability, hypocalcemia, hypophosphatemia, hyperphosphaturia, nephrocalcinosis (renal stones), and hypercalciuria[24,25]. While these biochemical abnormalities may not be of immediate importance to the health of the individual, long-term abnormal calcium metabolism (as indicated by hypercalciuria, nephrocalcinosis, and hyperphosphaturia) may result in osteomalacia[24]. Another possible factor contributing to osteomalacia concerns vitamin D. The results of an animal study showed that cadmium can interfere with the final activation of vitamin D_3 to 1,25-dihydroxycholecalciferol in the renal tubules[24]. Thus, depending on the degree of kidney damage, administration of vitamin D_3 and calcium may or may not lead to improvement in cases of osteomalacia. For example, Itai-Itai appeared to be a vitamin-D resistant form of osteomalcia[21]. However, in the few reported cases of osteomalacia in cadmium workers, administration of vitamin D_3 and other supplements resulted in improvement[1,7,24].

Anemia has been reported in workers exposed to cadmium fumes[20,21,25,61]. Its significance cannot be evaluated at this time.

Experimental animals which survive the acute pneumonitis that follows inhalation of cadmium fumes develop a perivascular and peribronchial fibrosis[6,8,60]. Cadmium-related fibrosis was not described in man[6,7,56,60] until a report by Smith et al. in 1976[57]. Chest X-rays showed mild to moderate fibrosis in cadmium-exposed workers. However, fibrosis in man is also related to tuberculosis, influenza, pneumonia, chronic bronchitis, pneumoconioses (e.g. silica, hematite, silicates, asbestos, coal, aluminium, beryllium, and tungsten). Occupational histories were not discussed.

Since Friberg's early work[19,20], there have been several reports of the occurrence of emphysema in cadmium workers[2,7,9,10,14,21,23,25,30,56]. These have been either autopsy studies[2,30,56] or cross-sectional (prevalance) studies of factory workers[7,9,10,23,25]. None of these studies took smoking habits into account. Furthermore, the diagnosis of emphysema in several studies[7,9,10,23,25] has been disputed[58]. Hence, it is still a matter of controversy whether chronic occupational exposure to cadmium produces emphysema. The concept of cadmium-induced emphysema is based on conclusions drawn in the older literature, and, in many instances, these conclusions have been accepted without any criticism.

Stanescu et al.[58] have critically reviewed the emphysema literature including the work of Friberg[20], Baader[2], Bonnell[7,9,10], Kazantzis et al.[23,25], Princi[50], Potts[49], Hardy and Skinner[22], Suzuki (see Stanescu[58]), Tsuchiya[61], Adams et al.[1], Lauwerys et al.[32], Smith et al.[56,57], and Lane and Campbell[30]. They concluded that either there is no causal relationship between chronic exposure to cadmium and emphysema, or that a mild form of obstructive lung disease affects some workers. This conclusion cannot be extrapolated to acute or subacute inhalation exposure[33,58].

Stanescu et al.[58] studied 18 workers who were exposed to a minimum of 50–356 µg of cadmium oxide dust/m^3 for 22–40 years (average of 32 years). The level of exposure was only a crude estimate. A control group was composed of 20 non-exposed workers, comparable to the exposed group on the bases of age, height, weight, and number of smokers and non-smokers. 33 of the 38 workers exposed and non-exposed were smokers or ex-smokers. However, the number of pack-years of exposure for the nonexposed workers was statistically significantly greater than that for the exposed workers ($p < 0.05$). Proteinuria (88–1740 mg/l) and cadmium concentrations in urine (27.5 µg/g creatinine) and blood (2.47 µg/100 ml) were significantly greater in the exposed group. Grade 1 dyspnea was more frequent in the exposed group, but no difference in the prevalence of other respiratory symptoms was found. The authors suggested that the increased reporting of dyspnea may have been motivated by a desire for compensation for occupational disease. There were only minor differences in lung function between the two groups. No emphysema was reported. This finding of no emphysema was supported by the results of earlier studies[1,22,31,50,57,58,61]. However, the designs of these negative studies were such that the authors may have viewed survivor populations, and those more susceptible to the effects of cadmium may have already disappeared from the work force and possible observation. The autopsy and prevalence studies published to date do not permit conclusions to be drawn regarding the relationship between cadmium exposure and emphysema. Retrospective and historical-prospective epidemiological studies of cadmium workers are needed.

Association with cancer

No conclusive data have been published regarding cadmium-induced cancer in humans[27]. In 1965 Potts[49] reported on 8 deaths in a group of 70 battery workers exposed for more than 10 years to cadmium oxide dust. 3 deaths were due to prostatic cancer, 1 due to bronchial carcinoma, and 1 due to carcinomatosis. Neither autopsy confirmation nor smoking habits were discussed. Definite conclusions cannot be drawn from a study with so few cases and no control group.

Kipling and Waterhouse[26] studied the same battery plants as Potts (see Malcolm[39]). All 248 employees and ex-employees with more than 1 year of exposure were included. There were 12 deaths due to carcinoma. Only the 4 deaths due to carcinoma of the prostate were significantly greater ($p = 0.003$) than the number expected (0.58, calculated from a regional cancer register). The number of observed cases of prostate cancer were too small to permit firm conclusions. Neither autopsy confirmation nor smoking habits were discussed. Malcolm[39] reviewed the Kipling-Waterhouse study[26] and reported that causes of death were not confirmed by autopsy and that the

4 men thought to have died of prostatic cancer had been exposed to cadmium oxide dust and nickel hydroxide, powdered nickel, and ferric hydroxide. However, Malcolm expressed doubt that nickel could be related to prostatic cancer, because the association had never been observed in the nickel industry.

Lemen et al.[34] returned to the same smelter Princi[50] had studied 30 years earlier. However, instead of using a cross-sectional design, Lemen et al. used a much more sensitive historical-prospective design. Employment histories were obtained for 292 white male cadmium workers who had at least 2 years of employment in the plant between January 1, 1940 and December 31, 1969. Vital status follow-up was continued through January 1, 1974. Comparison was made between the observed number of deaths among the study cohort and that expected by use of age, calendar-time, and cause-specific mortality rates for the total U.S. white male population. Lemen et al. found a significantly increased mortality due to total malignancies (27 observed vs 17.5 expected, $p < 0.05$), lung cancer (12 vs 5.1, $p < 0.05$), and prostatic cancer (4 vs 0.88, $p < 0.05$, for a latency period ≥ 20 years). Cause of death was primarily determined by interpretation of death certificates. There was no discussion of autopsy findings. Most of the excess risk for total malignancies was due to the lung cancer deaths. Smoking habits for these 12 men had not been obtained. However, histologic cell type was available for 8 bronchogenic carcinomas: 1 was undifferentiated small cell, 3 were anaplastic, 3 were squamous cell, and 1 was an oat cell carcinoma. No interpretation of this cell type information was made. The number of prostatic cancers were too small to allow definite conclusions to be drawn. As a footnote to this study, it is interesting to note that a long-term cadmium injection study of rats did not show any tumors in the prostate[36].

Kolonel[28] carried out a case-control study wherein 64 patients with renal malignancies were compared to 2 control groups, 72 patients with colon cancer and 197 with non-malignant gastrointestinal diseases. The 3 groups were well-matched for age (50–79), race (white), sex (male), computed dietary intakes of cadmium, smoking habits, interviewer bias (cases and controls were admitted and interviewed under the same tentative diagnosis of malignant tumor), and socioeconomic status. A person was considered to have had potential occupational exposure to cadmium if he had worked 1 or more years at a high-risk job within a high-risk industry (electroplating, alloy-making, welding, manufacture of storage batteries). Herein lies a major weakness in this study. Since there was no exposure data, there was no way of knowing how many patients were misclassified as to possible cadmium exposure. A statistically significant association was found between renal cancer and probable occupational exposure to cadmium ($p < 0.05$). It is notable that similar significant associations were found when the renal cancer cases were compared to either control group. Hence, the association with potential cadmium exposure appears to be specific for renal cancer but not all types of cancer. The association was even stronger between renal cancer and the combined affects of probable occupational exposure and smoking ($p < 0.01$) Hence, synergism between smoking and occupational exposure to cadmium was suggested. This possiblity is reasonable given the cadmium content of cigarettes referred to earlier.

Kjellstrom et al.[27] reported on new cases of cancer (1959–1975) in 228 cadmium-nickel battery workers. This group comprised all workers with 5 or more years of exposure to cadmium. Workers had been exposed to dusts of cadmium oxide and nickel hydroxide. Cadmium levels ranged as follows: before 1947, 1 mg Cd/m^3; 1950's, 200 µg Cd/m^3; 1962–1974, 50 µg Cd/m^3; since 1974, 5 µg Cd/m^3. Expected numbers of cancers (prostate, lung, kidney, bladder, colon-rectum, pancreas, nasopharynx, other, and all sites) were calculated using the life-table method and national average incidence rates. Out of the 9 cancer categories, only the observed number of new cases of nasopharyngeal cancers was statistically significantly greater than expected. However, this finding was based on the observation of only 2 cases, and caution is advised in interpreting such a small number (the negative findings also were based on very small numbers of observed cases). An unusually high occurrence of cancer of the nasal cavity has been reported among nickel smelter workers[27]. Kjellstrom et al. point out that the battery workers had been exposed to higher levels of nickel hydroxide dust than cadmium oxide dust. Finally, Kjellstrom et al. did not discuss smoking habits.

Chromosome aberrations may be related to the development of cancer and/or the inheritance of potentially undesirable traits. Several chromosome analyses have been conducted on the peripheral leucocytes of cadmium workers and Itai-Itai patients[4,12,16]. Contradictory results have been obtained, and it is not possible to draw firm conclusions at this time, especially since there were simultaneous exposures to lead and cadmium[4,16].

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