CADMIUM: BIOLOGICAL EFFECTS AND OCCURRENCE IN THE ENVIRONMENT

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It is only in recent years that there has been concern with cadmium as an environmental contaminant. Although the acute toxic properties of the soluble salts were known over one hundred years ago, the total usage was small, mainly as insoluble pigments. The recognition of its valuable metallurgical properties, such as corrosion resistance, led to increased metal production after 1910 from about 100,000 lb per year to 31,000,000 lb per year in 1968. Exposure of workers to the fumes of the oxide was recognized to be the cause of an acute and sometimes fatal pulmonary edema.

In 1950, Friberg (1) called attention to renal disease and emphysema in workers exposed to cadmium oxide dust over long periods in a battery plant. About this time, Japanese physicians were studying a unique disease in elderly women who had borne many children. The disease was characterized by osteomalacia, proteinuria, and glycosuria. These women had lived for many years in an area contaminated by mine drainage. It was concluded that the disease had been caused by a greatly increased intake of cadmium and possibly other metals in water and rice, plus a low calcium and Vitamin D intake, stresses of pregnancy and lactation, etc. The disease was reported in the English literature about 1969 by Tsuchiya (2) and was called Itai-Itai (ouch-ouch) disease, because of the severe bony pain.

In the meanwhile, biochemical and toxicologic studies had shown that the very small amount of cadmium (Cd) normally absorbed tended to be retained for long periods, particularly in the kidney, and proteinuria was noted when kidney concentrations reached a certain level. The discovery of a specific Cd and Zn binding protein in the liver and kidney and of various interactions between Cd, Zn, and Cu led to a great interest in cadmium toxiocology and to consideration as to the role it might play in diseases such as hypertension.

As a consequence of all the above complex and interesting findings, a very large literature on cadmium has appeared in the past few years. Much of it has appeared

in abstract form or in conference reports, project reports, etc. Fortunately, several comprehensive reviews have appeared in the past three years covering virtually all aspects of the subject.

One of the objectives of this review is to direct the uninformed reader to these sources of information. Another will be to discuss a few selected aspects of current research on cadmium, especially as it relates to sources in the environment.

REVIEWS AND SOURCES OF INFORMATION

Some brief comments on the coverage of some recent reviews may be helpful.

Friberg et al were pioneers in the study of chronic effects of cadmium and have provided especially comprehensive and critical evaluation (through 1972) of all aspects of its effects on man and animals. In their volumes on cadmium in the environment (3, 4) the Japanese studies are covered in detail. Based on the concept of a critical organ (kidney) concentration, an attempt is made to extrapolate from data on absorption from environmental sources and kinetics of uptake and excretion to a safe daily intake. Ecological aspects and analytical methods are covered briefly.

Chapter four, "Cadmium" in *Metallic Contaminants and Human Health* by Fassett (5) is a short review covering much the same material as in Reference 3. Coverage is through 1971. Somewhat more attention is given to ecology. It is best suited as a brief introduction to the subject. The suggestion is made that because of the differences in the electronic structures of mercury and cadmium, the latter would be less likely to form stable carbon bonds or to build up in the food chain.

"Cadmium Pollution in Perspective" by Yamagata & Shigematsu (6) is a succint review of the Japanese government investigations of cadmium contamination and Itai-Itai disease. Details are given of the extensive chemical studies made of the pollution of water, soil, and foods. The report illustrates the difficulties of extrapolating from present environmental conditions to those that may have existed when the disease was at its peak, some thirty years previously.

"Biochemical Effects of Mercury, Cadmium and Lead" by Vallee & Ulmer (7) provides a large number of references to the action of cadmium in enhancing or inhibiting various enzymes. Substitution of metalloenzymes, eg Zn, and binding to sulfur-containing proteins such as metallothionein, may play an important role in its biological effects.

"Environmental Impact of Cadmium" (8) provides much information on industrial uses and sources, geochemistry, and transport in the environment, as well as on biological effects and uptake and concentration in terrestrial animals.

Cadmium-The Dissipated Element is a monograph which examines in great detail the chemistry, technology, and environmental flow of cadmium. Many suggestions are made in the area of needs for future research and possible methods of control (9).

Two progress reports from the Oak Ridge National Laboratory (10, 11) on the ecology and analysis of trace contaminants consist of 900 pages and cover work now being done with support from the National Science Foundation. Much new informa-

tion is becoming available and attempts are being made to develop models for environmental transport.

OCCURRENCE AND DAILY INTAKE FROM ENVIRONMENTAL SOURCES

Cadmium is one of the rarer elements in nature, and it frequently occurs in combination with zinc in a zinc/cadmium ratio of about one hundred. Considerable attention has been given to its occurrence and possible daily intake in recent years. The facts have been summarized in several comprehensive reviews (3, 4, 8, 9). The earth's crust averages only 0.15 ppm, marine waters about 0.15 μg/liter, fresh waters less than 1 ppb, and air about 0.002–0.02 μg/m^3. Food intake varies but the mean is generally thought to be about 50–60 μg/day.

Although comprehensive balance studies in man (such as those of Kehoe on lead) are lacking, it is possible to make some estimates of man's total intake from food, air, and water, and of assimilation into the body from these sources. Based on the assumption of 6% absorption from the gut and of a 40% lung retention, estimates of the amounts assimilated by three general exposure groups of US adults are given in Table 1. Food and heavy smoking would be the largest single sources of assimilation according to these estimates (8).

Cadmium is also a relatively rare element in living matter. For example, the body burden of a 50 year old US adult has been estimated at only 30 mg (3, 4). There appears to be geographical variation, with European values somewhat lower and Japanese values higher. The estimates are, however, based on relatively sparse autopsy data and on extrapolations from amounts in the liver and kidney, which are thought to contain 50–75% of the body burden.

Terrestrial, marine, and fresh water animals also appear to have low levels with most of the cadmium in the liver, kidney, or digestive glands. Some marine animals have a remarkable ability to concentrate cadmium above the very low levels in sea water, e.g. oysters which have a concentration factor of 3 X 10^5. Higher levels in some cases may have resulted from pollution. There appears little evidence thus far for a concentration of cadmium in marine food chains.

Table 1 Estimation of the daily assimilation of cadmium by US adults (μg/day)[a]

	Source of exposure			
Exposure group[b,c]	Air	Food	Water	Total
A	0.02	2.0	0.1	2.12
B	0.16	2.0	0.1	2.26
C	2.0	2.0	0.1	4.1

[a] Assumptions: 6% absorption from gut. Inhalation of 18 m^3 air per day with 40% lung retention.

[b] No occupational exposure.

[c] A = nonsmoking, non-urban resident; B = nonsmoking, urban resident; C = smoker (2 packs/day), urban resident.

Plants also have low concentrations, generally less than 1 ppm dry weight (8). They are able to take up cadmium from the soil, somewhat in relation to the levels in soil.

ENVIRONMENTAL TRANSPORT OF CADMIUM

Information has begun only recently to appear on this subject. Much of this has been reviewed in publications of the Oak Ridge National Laboratory (9–11) and by the Panel on Hazardous Trace Substances (8). Attempts have been made to predict the importance of natural vs man-made origins of cadmium in the air, soil, and waters, the distribution in particles of various sizes in air, the proportion carried by waters in particulate form vs that in solution, and the occurrence in deposits or sediments in water.

Preston et al studied heavy metals in British coastal waters. There was little evidence of widespread pollution, and cadmium was highest in the North Sea. Other metals were higher in the East Irish Sea, presumably the more contaminated area. Two biological indicators were used, seaweed and the limpet. Seaweed showed little change in the decade 1960–1970. Limpet values were slightly higher in the contaminated areas. Cadmium contamination was limited to shoreline sections of contaminated areas. The percentage in particulate matter (greater than 0.2 μm pore size) was 16–20% for Cd, 70–93% for Cu, and 31–73% for Zn. The proportion of metal in suspended matter was fairly constant in relation to total concentration in time or space (12).

North Atlantic deep sea sediment averaged 225 ppb, with the higher levels formed in the mid-Atlantic ridge. There was no correlation with the carbonate content of sediment, indicating that shell Cd was relatively unimportant (13). A study of the heavy metal content of stream sediments in St. Catherine, Ontario, suggested that geochemical mapping may be used to reflect man's effect in an area (14).

Metals in the Amazon and Yukon rivers (Fe, Ni, Co, Cr, Cu, Mu) appear to be transported mainly as solids (rather than in solution) either as crystalline solids, as a metallic coating on particles, or as organic solids. The same distribution of metals among the types of solids was found in both rivers (15). No data was given on cadmium, but it seems likely that transport mechanisms would be similar.

An analysis of cadmium transport in the Mississippi-Missouri river systems (8) suggests that relatively large amounts might be arising from mine drainage, but there are anomalies in the expected Zn/Cd ratios if this were the case.

Sewage sludge appears to contain relatively large amounts of cadmium, the origin of which is not clear. Estimates indicate that its atmospheric washout and surface runoff may account for this (8). Acid rain, resulting from increased acid sulfates or nitrates in air may also increase soil leaching and account for some increase in sewage sludge (16). A National Academy of Sciences report (17) suggests that on a global basis, the input to the ocean from atmospheric washout is about twenty times greater than from river transport to oceans.

The major sources of Cd in air appear to arise from smelters, metal processing furnaces, and coal and oil burning. As in the case of water, there is only sparse

information on the chemical forms of Cd in air. There is considerable evidence that a number of metals, including Cd, are concentrated in smaller, respirable particles (18–21).

Studies now in progress of trace elements in East Tennessee ecosystems may in time provide a better picture of the possibility of a buildup in the food chain of terrestrial animals (9–11). For example, earthworms appear to be able to concentrate Cd and Zn from soil, but are unable to do so for Pb. They may aid in the penetration of some metals from surface litter vertically into soil cores. The behavior of Cd in an invertebrate food chain has been evaluated in crickets (primary consumers) and spiders (predators) using ^{109}CdO and ^{109}Cd(NO3)2. Crickets, feeding on tagged vegetation, accumulated Cd rapidly, but did not concentrate it above the food source level. On the other hand, spiders feeding on the exposed crickets accumulated and excreted Cd slowly. They did not concentrate it above that in the food level (crickets). The half-life in spiders appears quite long, similar to that in vertebrates.

Studies in an avian food chain (sparrows fed ^{109}Cd-tagged seed) showed a relatively long half-life with 84% of the body burden (excluding the gut) found in the kidney and liver. The amount of Cd assimilated from food was only about 8% of that available. There was no concentration above the level in the food source in the duration of the study. In some respects the sparrow appears similar to mammalian species.

EFFECTS ON THE KIDNEY

Hypertension

Evidence for a possible relation of Cd to hypertension has been reviewed (3, 8, 9). This was based primarily on a series of autopsy studies showing increased Cd or Cd/Zn ratios in the kidney of hypertensive subjects. Rats or rabbits were also said to develop hypertension following Cd treatment.

However, others have not found increased Cd levels in hypertensives (22). Hammer et al (23) found no evidence of hypertension in workers exposed to Cd containing superphosphate dusts. No hypertension has been observed in workers by others (3) even when exposures were sufficient to cause renal damage and proteinuria. The original autopsy studies were confounded with respect to smoking, age, sex, renal pathology, and cause of death (23). The decrease with age in kidney weight and in the ratio of parenchyma to stroma may have affected the concentrations found in such studies.

Rats given relatively high levels of Cd in drinking water for sixteen weeks showed decreased systolic blood pressure, contrary to previous reports (24). Vascular smooth muscle characteristics from rabbits and dogs treated parenterally with Cd have been examined and are said to show differences in in vitro response of aortic strips to vasopressor agents in some cases (25, 26). Cd at a level of 100 ppm in rat drinking water resulted in a lowered contractile response of aortic strips of Cd in vitro (27). Some changes were noted in tissue distribution of Cd and Zn in Cd hypertensive dogs (28) following parenteral injection of Cd. Hypertension in rats given Cd at 10 ppm in drinking water was said to be prevented by 3.5 ppm selenium

in the water. Whether this was the result of formation of CdSe (insoluble) in the water was not stated. The degree of hypertension produced was very slight, however, and these results seem questionable (29). The failure of various epidemiologic studies to confirm a clear relation between Cd intake or tissue levels and hypertension or cardiovascular disease makes the hypothesis doubtful (30–34).

Renal Effects

The interest in renal effects (aside from hypertension) arises mainly from two sources, the appearance of proteinuria of a low molecular weight type after long exposure to excessive concentrations of Cd by inhalation, and the storage of Cd in the kidney in the form of Cd binding proteins (CdBP) known as metallothionein (3, 4, 33). The proteinuria is considered to be the first sign of tubular dysfunction and is said to occur when renal cortical levels of Cd reach about 200 ppm (wet weight) compared to normal levels of about 50 ppm in adults (4). Renal cortical Cd appears to rise from about zero at birth to 50 ppm in adults, followed by some decline after 50 years of age (3, 35). Zinc seems to parallel Cd on a molar basis as regards storage in the kidney, but additional mobile Zn is also present (35).

Livingstone (36) has shown a rather steep gradient in concentrations of Cd and Zn from the outer cortical layers to the medulla. The lack of a homogeneous distribution requires that very great care be used in sampling and comparing data. The primary period of rapid renal accumulation is said to be in the first three years of life, during which time the Cd levels rise some 200 times (37). The fact that the fetal kidney does not undergo glomerular filtration may explain the low levels at birth. As more nephrons become active in early life, more Cd becomes stored in the cortex as CdBP. The same mechanism may account for the storage of Zn or some other metals (36). Much more information is needed on the buildup in the first two decades of life, and also on Cd intake and excretion in this period.

Functional effects on the kidney have been examined (38). The infusion of $CdCl_2$ in dogs (plus cysteine to prevent effects on blood pressure etc) caused a drop in the Na excretion and increased reabsorption of Na in the proximal tubule. However, when Cd was given in the renal artery in the form of ^{109}Cd metallothionein, there was no effect on renal tubular transport of Na, nor on blood pressure, renal plasma flow, or glomerular filtration rate. Large fractions of the Cd metallothionein were retained by the kidneys and more than 30% excreted in the urine (39).

$CdCl_2$ iv plus mercaptoethanol caused some inhibition of amino acid transport in rabbit kidney and also of dicarboxylic acids (40). The filtration, excretion, and uptake of ^{109}Cd by the rabbit kidney is markedly affected by the presence of different chelating agents, such as mercaptoethanol or EDTA (41). Studies of this type and those mentioned above emphasize the need to know the exact form in which Cd is present in environmental exposures.

In addition to proteinuria, a previous report had indicated that an increased excretion of certain amino acids resulted from Cd exposure. Goyer et al examined urines of Japanese workers exposed to Ag and Cd during smelting of alloys. Cd levels in air were about 130 $\mu g/m^3$. Cd excretion in urine was about 170 $\mu g/l$ and

no relation was found to proteinuria, nor was there increased excretion of specific amino acids (42). Friberg et al have reviewed various other attempts to elucidate the mechanism for renal damage and its relation to critical levels in the kidney (4). In general these studies have confirmed their previous findings that about 200 ppm in the renal cortex is a critical level, but the toxic mechanism remains obscure.

EFFECTS ON CARBOHYDRATE METABOLISM

In addition to proteinuria, some cases have shown glycosturia; this has been thought to be of renal origin. Glucose tolerance curves in rats getting 17 μgCd/ml of drinking water for 4 weeks (zinc and copper levels were varied) varied directly with serum and dietary Zn levels. Cd tended to lower serum zinc. Glucose tolerance was affected. Insulin levels also varied with Zn levels. These adverse effects of Cd were prevented by increasing Zn intake (43). Rats given $CdCl_2$ ip at 1 mg/kg daily for 45 days showed a drop in hepatic glycogen and increased blood glucose and urea. Four enzymes involved in gluconeogenesis appeared to increase in the liver and renal cortex. The changes persisted for a month (44). It is difficult to interpret such studies in the context of human exposures which thus far have not suggested any direct effects on carbohydrate metabolism.

CADMIUM BINDING PROTEINS (CdBP)

Much attention is being given to CdBP because the nature of the binding appears of critical importance in the understanding of metabolism and in interpretation of toxic effects.

The subject of biliary excretion of Cd has had little attention previously. Vostal et al (45) have noted that $^{109}CdCl_2$ given iv in rats is excreted in the bile in proportion to the dose. The retention in the liver is in proportion to the dose up to 1 mg/kg; at higher doses bilary excretion predominates. Under these conditions the biliary Cd is in the form of glutathione complex, and Cd in liver and kidney supernatants is bound to high molecular weight proteins.

When CdBP were induced by injection of Cd 24 hr previously, liver retention increased and biliary excretion decreased. The Cd was now bound to low molecular weight proteins in liver and kidney supernatants (46). Significant amounts of a Cd-cysteine adduct were seen in the urine. In other words, these studies show that induced synthesis or dosing with CdBP have profound but completely different effects on the distribution and excretion of Cd. Chen et al (47, 48) have examined CdBP in relation to testicular damage in the rat, using $^{109}CdCl_2$. Binding appears to be present in the testis to both a low (10,000) and a high molecular weight (30,000) protein. Pretreatment with $Na_2{}^{75}SeO_3$ prevented the damage but doubled the uptake of Cd in the testis, and shifted the binding to the higher molecular weight protein.

These studies, together with those of Vostal et al (45), suggest that it is unlikely that correlations can be made directly with the quantities of Cd present in damaged tissues, but that the nature and properties of the bound fractions are essential.

In addition to the evidence for CdBP in vertebrates and invertebrates, such proteins are found in microorganisms (49). It is obvious that they have a great "evolutionary antiquity." The mutually antagonistic effects of Cd and Zn seen in vertebrates extend to lower organisms as well (50). CdBP may also bind other metals, e.g. Hg (51). Pretreatment of rats with Cd caused a threefold uptake of ^{203}Hg by the induced CdBP. Other studies on binding have appeared but are not reviewed here (52–56).

CADMIUM EFFECTS IN RELATION TO ZN, CA, CU, AND OTHER METALS

It has been known for some time that Cd effects can be profoundly altered or abolished by Zn, Se, and Ca in experimental studies, although with the possible exception of Ca, this has not been established for humans. The relations between Cd and Zn in the rat and mouse liver, kidney, pancreas, and testis have been examined by simultaneous injection of ^{109}Cd and ^{65}Zn. The time concentration curves appear quite different with Zn being more mobile (57). Under these conditions the Zn attached to the CdBP was depleted in a week, whereas Cd was fixed (58).

Cd effects on Zn and Cu have been studied in a variety of species including rats, quail, and ruminants. The doses of Cd used were generally relatively large. In most cases, the effect was to depress Zn and Cu (59–64). The hypochromic anemia from Cd may be related to effects on Fe metabolism (65–67). Miller (68) has given a cogent discussion of these complex interactions.

The effects of Cd on calcium metabolism with respect to uptake (69, 70), renal tubular effects (4), parathyroid effects (71), and on Vitamin D synthesis (72) have been examined. No conclusions seem possible at this point because of conflicting data and varying procedures, but some effects were noted in all studies.

OCCUPATIONAL EXPOSURES

Very little new information has appeared since that reviewed in references 4, 8, and 9. Lauwerys et al (73, 74) have reported on pulmonary function, Cd levels in blood and urine, various enzyme tests, and protein excretion in workers exposed to relatively low levels over varying periods of time. The changes in pulmonary function were relatively small. Excretion of Cd in the urine was lower in nonsmokers, but blood levels were not affected. Coal workers pneumoconiosis was evidently not related to Cd levels in coal since the Cd content of coal was the same in mining areas with the lowest and highest incidence of the disease (75). All other metals were higher in coal from areas of higher incidence, however.

CARCINOGENIC STUDIES

Reports of increased prostatic cancer in small numbers of exposed workers (76, 77) have not been followed by other reports of increased cancer in man from exposure.

Malcolm states that it does not cause cancer of the prostate in man (78). Levy et al (79) were unable to find any evidence for cancer of the prostate in rats given subcutaneous injections for a lifetime. There was a low incidence of fibrosarcoma at the injection site, however. Cancer was not related to long-term feeding of rats and dogs (8). Sunderman (80) reviewed metal carcinogenesis and pointed out that many metals that are carcinogenic at the site of injection are not so when given orally. Zinc appears able to prevent Cd carcinogenesis in the rat testis (81). Cadmium was not a mutagen in the mouse by the dominant lethal assay (82). Although the evidence for carcinogenesis appears doubtful, further studies are in order.

ITAI-ITAI DISEASE

Friberg et al (4) has described the extensive epidemiological studies now being done in Japan in Cd-polluted areas. The disease as such seems to have disappeared even though there are a number of areas where the estimated Cd intake is relatively high. Emphasis at present is on the possible relation of Cd intake and excretion to proteinuria. Proteinuria seems to be more prevalent than in some other countries and to increase with age. Because of methodological difficulties in such large-scale studies, there are conflicting data in relation to exposure and effects in different areas. A study of translations of voluminous reports by the Japanese Public Health Association[1] leaves one impressed with the breadth and scale of the investigations. However, the relation of proteinuria to exposure seems even more tenuous than that described by Friberg. This may be clarified in the future as methodology improves. There appears to be little information on the extent and type of proteinuria in relation to racial or geographic factors on a world-wide basis.

DISCUSSION

In the attempt to understand the tangled and complex situations in cadmium research, it appears that research in four areas would help to clarify the situation.

1. Study of Cd complexes as they occur naturally in food are essential. For example, arsenic occurring in fish, or Zn in corn, have been shown to have different metabolic fates than when given in pure chemical form (83, 84). These findings, together with those of Vostal and Chen discussed previously, make it clear that interpretation of toxic effects will be difficult unless naturally occurring sources are used. Also, a large amount of research has involved parenteral injections with the probability of different forms of binding or distribution than seen with oral routes. Single doses may fail to involve the induction of CdBP.
2. Interactions with Zn, Cu, Ca, and possibly Fe will almost certainly be at the heart of any future understanding of Cd effects.

[1]The author is indebted to Dr. Robert Horton of The National Environmental Research Center for an opportunity to review these reports.

3. There is a lack of a comprehensive balance study on humans, using naturally occurring Cd sources, and variable intakes, similar to the classical studies by Kehoe on lead (85).
4. Occupational studies, with long-term data on exposure levels, smoking, dietary and water intake, and blood and urine levels, pulmonary and renal effects, carcinogenic effects, etc, would in time settle many of the present uncertainties.

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