

Dietary Exposure to Cadmium and Health Effects: Impact of Environmental Changes

by Magnus Piscator*

Cadmium exposure, metabolism, and effects are described especially in relation to dietary intakes. Data on dietary intakes in several countries have been compiled from studies using the duplicate diet method or fecal analysis. These two methods seem to give more accurate data than estimates based on cadmium concentrations in food classes and food consumption (composite method). The present data on absorption and retention of ingested cadmium indicate that normally less than 5% is absorbed, but absorption may increase in women who have iron deficiency. Earlier estimates of the critical concentration in renal cortex being about 200 mg/kg wet weight still seem to be valid. New information is available on present renal levels and their distribution in the general population. The present margin of safety with regard to risk for renal effects is small.

To predict future health risks from increases in dietary cadmium due to environmental changes such as acid deposition, it is necessary that the models used are based on correct assumptions. Of interest are the distributions of dietary intake, gastrointestinal absorption, and renal cadmium concentrations. These distributions are normal or lognormal, and since standard deviations are used when estimating risks, it is of paramount importance that the standard deviations are estimated as accurately as possible. At present it is not possible to quantify the effects attributed to acid rain only; account must also be taken of cadmium added to, e.g., soil by use of sewage sludge and other fertilizers.

In addition to risks to human health, cadmium also poses a threat to horses, which generally have renal cadmium concentrations several times higher than adult humans. It is recommended that horses should be monitored in areas where acid deposition is high. Such monitoring might provide valuable information about impact of acid rain.

Introduction

In 1950 Friberg reported on the chronic effects of occupational exposure to cadmium, lung and kidney disease being the main features (1). For two decades most research concentrated on occupational effects of cadmium. When it became known in the 1960s that dietary cadmium exposure could have health effects, especially tubular disease (2,3), the main interest was focused on cadmium in the general environment.

During the last decades much information has been collected in regard to exposure levels of cadmium as well as metabolism and effects. The perfection of analytical methods capable of accurately determining even small amounts of cadmium in exposure media and body fluids, together with the development of sensitive methods for detecting renal effects, have made it possible to construct dose-response relationships. Dose-response curves based on response in relation to internal doses of cadmium (4) are relatively accurate, whereas the response in relation to external exposure, e.g., via air or food, is not as well described.

Increased knowledge about gastrointestinal absorp-

tion of cadmium, biological half-life, metallothionein, etc., has also made it possible to develop models for cadmium metabolism in human beings (3,5). These models have been used to predict the effects of exposure to cadmium (6). Each year considerable amounts of cadmium are deposited on agricultural lands and gardens by the application of phosphate fertilizers and sewage sludge and by wet and dry deposition (7,8). Recently, there has been growing concern that acid rain may increase the availability of cadmium in soil and thus cause further increases in cadmium concentrations in agricultural products.

In the following, a brief overview will be given of exposure levels, metabolism, effects and dose-response relationships, with emphasis on dietary exposure to cadmium. For more information on the general toxicology of cadmium in human beings, reference is made to a number of extensive reviews (3,9-12).

Exposure

For the general population, the main exposure to cadmium is via food (3). Generally, only minor amounts will be inhaled from ambient air (3). The average daily intake via water is less than 1 µg in homes with copper pipes and 1 to 2 µg in homes with galvanized pipes (13).

*Department of Environmental Hygiene, Karolinska Institute and the National Institute of Environmental Medicine, Stockholm, Sweden.

Tobacco is generally grown on relatively acid soils, and since cigarettes contain cadmium (3,14-16) smokers will get an additional exposure, which in a heavy smoker may cause an absorption of similar amounts as from food (3,14-16).

Table 1 summarizes some studies on dietary intake of cadmium in different countries. In addition to the sampling methods shown in Table 1 (duplicate diet and fecal analysis), there have also been several estimates based on cadmium concentrations in different foods and the consumption of these foods, e.g., the market basket studies in the U.S. These estimates are generally somewhat higher than those shown in Table 1. It should be noted that in all the duplicate diet studies the mean and range were based on all diets analyzed, not on individual means as were the studies using fecal analysis. Thus, in the duplicate diet studies in New Zealand and Sweden the number of participants was 23 and 24, respectively, and the number of diets obtained from each participant varied from 3 to 21 for New Zealand and 1 to 4 for Sweden. In the fecal studies the mean was based on individual means of 3-day collections in Sweden and 5-day collections in the Japanese studies.

Regarding the U.S. study (23), single fecal samples from 211 subjects in Chicago showed an average of 13.4 $\mu\text{g}/\text{day}$ (range 0.6-85.2 $\mu\text{g}/\text{day}$), whereas in 63 subjects in Dallas (mean of two days) the mean was 13.7 $\mu\text{g}/\text{day}$ and the range 4.7 to 32.6 $\mu\text{g}/\text{day}$. The distributions are generally skewed, but this mainly due to the small number of determinations for each individual mean. Thus the range will become more narrow, and the standard deviation will become smaller if the individual means are based on a larger number of collections. However, there are no data on individual variations and population ranges over longer periods of time.

Estimates from several countries show that vegetables, potatoes, and cereals generally form a major part of the dietary intake (3,7,8,10). Dairy products and meat are minor sources, whereas liver and shellfish may sometimes contribute significantly (18,24).

Metabolism

The absorption or retention of ingested radioactive cadmium has been studied in experiments carried out with volunteers. As shown in Table 2, the range seems to be wide in some studies, but it should be noted that iron deficiency has been shown to have a profound influence on absorption of cadmium (25,26). Some of the differences between the studies may also depend on the time of observation after exposure and the vehicle, i.e., kidney, milk, or crab meat. The data indicate that, generally, less than 5% of an ingested dose is absorbed. Also deficiencies in calcium, vitamin D, and protein may increase the absorption (3).

There are no data on individual variations in absorption over longer periods. Women are more susceptible to iron deficiency during the fertile period of life. In developed countries it is unlikely that there are people who would have an average absorption above 10% during a whole lifetime.

Initially, cadmium will be taken up to a large extent by the liver, where most of it is bound to metallothionein (3,29). There will be a continuous synthesis and degradation of metallothionein, a process which keeps cadmium effectively trapped in the liver. Cadmium is only slowly released from the liver, the biological half-life probably being around 10 years (5).

Metallothionein has been found in plasma, and due to its low molecular weight it can easily pass the glomerular membrane. Metallothionein will be reabsorbed in the proximal tubules and thus cadmium passes into the renal tissue. The kidneys can also synthesize metallothionein, and, as in the liver, continuous degradation and synthesis of the protein will keep cadmium stored there for a long time (29). Biological half-life in the kidneys is more than 10 years (5). The whole body biological half-life has been estimated to be 20 to 30 years (3).

The newborn is virtually free from cadmium, the placenta being an effective barrier (3). With time, the highest cadmium concentrations will be found in the kidneys;

Table 1. Dietary intake of cadmium.

Country	Sex	n	Method*	Age	Cd, $\mu\text{g}/\text{day}$				Reference
					Mean	SD	Median	Range	
Belgium (urban)	F	124	D	30-65	18.0	13.1	14.6	2-88	(17)
New Zealand (urban)	F	179	D	19-50	21.0	14.0	17.5 ^b	5-118	(18)
Sweden (rural)	M	21	D	68-69	12.9	6.2	12.5 ^b	6-35	(19)
	F	29	D	68-69	13.0	15.2	7.5 ^b	4-86	
Japan (Tokyo)	M	19	F.A.	20-29	35.0	16.8	28.4	11-72	(20)
	F	17	F.A.	20-29	24.5	11.0	22.6	12-50	
Japan (urban)	M	7	F.A.	20-29	56.4	13.0	53.8	41-79	(21)
Sweden (Stockholm)	M	10	F.A.	20-29	18.2	8.6	16.3	7-35	(22)
	F	10	F.A.	20-29	14.6	10.0	12.4	7-40	
USA (Dallas, Chicago)	M + F	274	F.A.	20-59	13.5			0.6-85.2	(23)

* D = duplicate diet; F.A. = fecal analysis.

^b Estimated from distribution curves.

Table 2. Absorption of cadmium after ingestion: human subjects.

Sex	n	Absorption, %			Reference
		Mean	SD	Range	
M	7	2.5	1.0	1.1-4.1	(25)
F	5	3.3	2.6	1.4-7.0	
M	10	2.6	1.9	<1.0-7.0	(26)
F	12	7.5	6.2	<1.0-22.0	
M	5	5.9	1.0	5.4-7.0	(27)
M	7	2.7	2.3	1.2-7.6	(28)

about one-third of the body burden will be in the kidneys after long-term low-level exposure (3,5).

There have been many studies on renal concentrations of cadmium in human subjects. In most European countries and in North America the average concentrations in renal cortex at age 50 are 20 to 30 mg/kg (12,30,31). In Belgium and Denmark the concentrations are reported to be higher, around 40 mg/kg (12,31). Several studies in Japan have shown average concentrations of 60 to 100 mg/kg in areas regarded as not severely polluted by cadmium (12,30,31). Women generally have higher concentrations than men, which is consistent with the higher absorption shown in Table 2.

The above data refer to groups containing both smokers and nonsmokers. Nonsmokers have average concentrations of 10 to 20 mg/kg, and smokers may have twice as high concentrations. The cadmium concentrations are lognormally distributed, and in the studies mentioned above the highest concentrations found were about 100 mg/kg in Europe and North America, whereas in Japan, renal concentrations around 200 mg/kg have been found even in areas regarded as not being polluted by cadmium (30,31). Data obtained in two collaborative studies between several countries (31,32) show that the logarithmic standard deviation is generally about 1.75 in age groups from 20-29 to 50-59, smokers and nonsmokers together. Table 3 shows data from the latest collaborative study (31).

Urinary excretion of cadmium is slow, and nonsmok-

Table 3. Geometric standard deviations of geometric means for cadmium concentrations in renal cortex.*

Country	SD of cadmium concentration			
	Age 20-29	Age 30-39	Age 40-49	Age 50-59
Belgium	—	1.7	1.7	1.6
China	1.4	—	—	—
India	1.3	1.3	—	—
India	1.6	2.3	—	—
India	1.6	1.7	1.8	—
Israel	1.6	—	—	—
Japan	—	—	1.5	1.6
Sweden	1.9	1.9	1.8	2.3
Yugoslavia	—	1.9	1.8	1.8
Median	1.6	1.8	1.8	1.7

* From Friberg and Vahter (31). Only groups with $n \geq 10$.

ers in Sweden excrete on an average less than 0.4 $\mu\text{g/g}$ creatinine, whereas smokers excrete twice that amount (32). Urinary cadmium is related to body burden and is regarded as a reliable indicator of the internal dose of cadmium (4). More than 50% of the body burden will be in the liver and the kidneys. Even if concentrations in muscles are low more than 10% of the body burden is in that compartment (30).

Accumulation of large amounts of cadmium is not limited to humans. In Table 4 it can be seen that adult horses have renal concentrations of cadmium about five times those of adult nonsmoking humans. Much lower values for cadmium in horse kidney were reported in a study from the U.S. (38), but this study had several methodological problems (39). The horse has a unique capacity to absorb and accumulate cadmium, since other domestic animals have low cadmium concentrations in organs (38).

Effects

The kidney is the critical organ in long-term, low-level exposure to cadmium. The critical effect is a decrease in the tubular reabsorption of proteins and an increased excretion of low molecular weight proteins, tubular proteinuria (3). This effect may occur at a cadmium concentration of about 200 mg/kg wet weight in renal cortex (3,4). It has been estimated that about 10% of a population with this concentration may have slight proteinuria (4). Further accumulation of cadmium may cause a spread of the tubular lesion with decreases in the reabsorption of glucose, amino acids, phosphorus, and calcium (3). Disturbances in mineral metabolism may cause renal stones, as seen in male Swedish cadmium workers (1) or lead to osteomalacia (Itai-Itai disease) as seen in Japanese women exposed to cadmium via rice (3,9). Nutritional deficiencies, especially calcium and vitamin D deficiencies, contributed to the development of this osteomalacia, since males in the same area showed severe tubular dysfunction without marked bone changes (3,9).

Tubular dysfunction caused by cadmium is irreversible, but progress is only slight if exposure ceases (40). Glomerular function may be reduced, but severe uremia does not develop (40). Cadmium-induced tubular dysfunction is diagnosed by determination of urinary excretion of β_2 -microglobulin or other low molecular weight proteins, e.g., retinol-binding protein (41).

Renal effects have also been reported in horses exposed to cadmium (37). A mare and her foal developed nephrocalcinosis after eating forage from an area severely polluted by cadmium and zinc. The cadmium concentrations in renal cortex were 156 and 115 mg/kg for mare and foal, respectively. Since the kidneys were damaged the concentrations might have been higher when the damage first occurred. It has also been reported that slight morphological changes in horse kidneys are related to cadmium concentrations in the range of about 75 to 200 mg/kg (33).

Dose-Response Relationships and Risk Estimates

A relationship between internal dose and renal effects has been seen in studies on occupationally exposed people (4). Urinary cadmium has generally been used as an indicator of internal dose, but in a few studies *in vivo* determination of cadmium in the liver and kidneys has made it possible to obtain estimates of the amounts of cadmium in these organs (4). A confounding factor is that once renal tubular dysfunction has developed, urinary excretion of cadmium will increase and eventually lead to a decrease in renal cadmium. In severe cases, renal cadmium concentrations will be of the same magnitude as those found in normally exposed people (3). The best dose-response relationships have in fact been obtained by using liver concentrations of cadmium in occupationally exposed workers as dose indicators (4). In Table 5 it can be seen that at liver concentrations of 30 to 39 mg/kg, proteinuria appears in 10% of the cases. By determination of renal cadmium in workers without signs of renal dysfunction, it was possible to estimate the relationships between liver and renal cadmium. A liver concentration of 30 mg/kg corresponded to a renal cortex level of 216 mg/kg (42). This relationship cannot be used for the general population, since the ratio between liver cadmium and renal cadmium will be much lower in long-term, low-level exposure via food (3,30). The corresponding urinary excretion of cadmium is about 10 µg/g creatinine (4,42).

There have been several studies in Japan on the relationship between dietary cadmium and renal effects. Since it has not been possible to estimate earlier exposure, only recent exposure data could be used. Estimates of the daily dose needed to produce renal effects in Japan have varied from about 150 µg and upwards (3,6,43).

Several models have been used to estimate the dietary exposure that may cause cadmium concentration in renal cortex of 200 mg/kg. A one-compartment model was first used, and it was estimated that for a 70-kg person, a daily intake of about 250 µg cadmium was needed to reach the 200 mg/kg level. It was assumed that 4.5% of the intake was retained and that the biological half-time was 38 years. Assuming a half-life of

19 years gave an estimated dose of 350 µg/day. Changes in calorie intake during the 50 years were also included in the model (3). An important step was the development of a multicompartiment model (5). Eight compartments and 21 distribution coefficients were used to describe the flow of cadmium through the body. By changing the coefficients it was possible to adjust for metabolic changes in relation to age and different exposure situations. It was calculated that at age 45 a maximum average concentration of 200 mg/kg should be reached after an average daily exposure of 440 µg in a 70-kg person. Daily intake of cadmium was assumed to vary with age as does calorie intake. The gastrointestinal absorption was assumed to be 4.8%, the biological half-lives in liver and kidneys, 12 and 14 years, respectively. This model was shown to fit the empirical data well (5).

Estimates were made of the dietary intake needed for certain percentages of population to reach the critical level (6). As noted above, 440 µg/day would result in 50% above that level. Of interest for the present discussion are the estimates for low intakes. An average daily intake of 32 µg was estimated to result in 0.1% of a population having a concentration above 200 mg/kg in renal cortex. The corresponding value for a daily intake of 60 µg was 1%.

However, these estimates were based on the assumption that the geometric standard deviation for the mean concentration in renal cortex is 2.0. As seen in Table 3, it is more likely to be around 1.75, which means that the average intake needed for 0.1% of a population to reach renal concentrations above the critical level will be about 50% higher, i.e., on an average, 40 to 50 µg/day. This is more than twice the present intake in most countries and also agrees with the fact that the upper level for renal cortex concentrations is at present close to 100 mg/kg. In addition to exposure via food, a large part of the population absorbs cadmium from smoking. It should be noted that the estimates of distributions of cadmium concentrations shown in Table 3 are based on groups consisting of both smokers and nonsmokers.

Not only renal distributions of cadmium must be taken into account. The distribution of dietary cadmium intakes over longer periods is probably normal at pres-

Table 4. Cadmium concentrations in renal cortex from horses.

Country	n	Age	Cd, mg/kg (wet weight)			Reference
			Mean	SD	Range	
Sweden	5	1-4	31.9	20.0	12-63	(33)
	13	5-9	49.2	25.8	18-105	
	16	10-14	61.8	32.3	16-160	
	15	15-19	75.9	45.4	17-186	
	18	20+	72.3	30.3	31-151	
Norway	50	1-25	48.0	23.0	5-120	(34)
Denmark	7	12-39	33.6	8.7	25-48	(35)
West Germany	68	Not reported	43.5	53.0	0.8-370	(36)
Poland	40	Not reported	57.8	37.0	16-210	(37)
USA	5	Not reported	28.0	18.0		(38)

Table 5. Relationship between liver cadmium level and prevalence of abnormal β_2 -microglobulinuria in a group of 148 workers.^a

Cadmium in liver, mg/kg	Number of workers	Prevalence of abnormal β_2 -m	
		Number	%
10-19	54	0	0
20-29	27	1	4
30-39	28	3	11
40-49	18	3	17
50-59	8	2	25
60-69	5	2	40
70-160	8	8	100

^aFrom Roels et al. (4).

ent in most countries, but may have been more skewed in the past, when food distribution systems were not so well developed and locally grown food was consumed more frequently. The biological half-life of cadmium must vary, but so far there are not enough data on this subject. Individual sensitivity in the kidney may play a role for the development of effects. Kidney sensitivity may be related to the metabolism of metallothionein and zinc. In fact, an effect of cadmium, which at low-level exposure cannot be regarded as adverse, is the increase of renal zinc, which parallels the increase in cadmium (44).

Effect of Environmental Changes

Dietary intake of cadmium may increase due to several factors. Estimates have been made of the impact of increased soil concentrations of cadmium on dietary intakes and the amount of cadmium in sludge or fertilizers which may be applied without adverse effects (7,8,45,46). Another factor is wet and dry deposition of cadmium from waste incineration and smelters, which at present contributes much less than sewage sludge and phosphate fertilizers.

Acid rain may cause a lowering of soil pH and thus an increase of the cadmium uptake in crops. In areas where roof catchment cistern systems are used, a decrease in pH may cause an increase in cadmium concentrations of drinking water. Some increase may also be expected where galvanized water pipes are used. From what was discussed earlier it is obvious that an increase in the dietary intake of a few micrograms might be tolerated in many countries, but in areas with average intakes of 50 μ g and higher, the percentage of people with concentrations above the critical renal level may increase if cadmium in the diet increases.

Models have been used to predict effects of cadmium applied to acid and neutral soils (8). Such models can also be used to predict changes due to pH changes alone, assuming that cadmium concentrations in soil are constant. It is unlikely that such conditions will exist in soils used for edible crops but are more likely to occur in areas where cadmium has not been added, i.e., in pastures where cattle and horses graze.

It may be of value to monitor horses in areas where

pH changes are expected. By examinations at intervals of 5 years it would be possible to detect increases in renal cadmium concentrations. It should also be kept in mind that horses are at greater risk than most human beings.

Conclusions

The present average daily intake of cadmium in most countries is 10 to 20 μ g and may be assumed to increase in the future due to increased soil levels of cadmium caused by the application of sewage sludge and phosphate fertilizers to agricultural land, to which may be added wet and dry deposition due to emissions from smelters, waste incinerations, etc. A decrease in soil pH may also cause an increase in dietary cadmium. Whatever the source, there is only a small margin for further increases in dietary exposures, since the renal concentrations of cadmium have already reached a level, where the margin of safety is small. In addition to dietary exposure there is exposure via smoking, which may also increase due to increases in soil Cd or pH changes, and allowance must be made for occupational exposure.

REFERENCES

1. Friberg, L. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. A clinical and experimental study. *Acta. Med. Scand.* 138: 1-124 (1950).
2. Tsuchiya, K. Causation of ouch-ouch disease (Itai-Itai byō). An introductory review. Part II. Epidemiology and evaluation. *Keio J. Med.* 18: 195-211 (1969).
3. Friberg, L., Piscator, M., Nordberg, G. F., and Kjellström, T. *Cadmium in the Environment*, 2nd ed., CRC Press, Cleveland, Ohio, 1974.
4. Roels, H. A., Lauwerys, R. R., Buchet, J.-P., Bernard, A., Chettle, D. R., Harvey, T. C., and Al-Haddad, I. K. *In vivo* measurements of liver and kidney cadmium in workers exposed to this metal: its significance with respect to cadmium in blood and urine. *Environ. Res.* 26: 217-240 (1981).
5. Kjellström, T., and Nordberg, G. F. A kinetic model of cadmium metabolism in the human being. *Environ. Res.* 16: 248-269 (1978).
6. Kjellström, T., Epidemiological aspects of the dose-response relationship of cadmium-induced renal damage. *Proceedings of the 2nd International Cadmium Conference Metal Bulletin* 1980.
7. Hutton, M. Cadmium in the European community: a prospective assessment of sources, human exposure and environmental impact. MARC Report Number 26. The Monitoring and Assessment Research Centre, Chelsea College, University of London, 1982.
8. Ryan, J. A., Pahren, H. R., and Lucas, J. B. Controlling cadmium in the human food chain: a review and rationale based on health effects. *Environ. Res.* 28: 251-302 (1982).
9. Tsuchiya, K., Ed. *Cadmium Studies in Japan: A Review*. Kodansha Ltd., Tokyo: Elsevier/North Holland Biomedical Press, Amsterdam; 1978, p. 376.
10. CEC. *Criteria (Dose/Effect Relationships) for Cadmium*. Commission of the European Communities. Pergamon Press, New York, London, 1978.
11. Friberg, L., Kjellström, T., Nordberg, G., and Piscator, M. Cadmium. In: *Handbook on the Toxicology of Metals* (L. Friberg, G. F. Nordberg, and V. B. Vouk, Eds), Elsevier/North Holland Biomedical Press, Amsterdam, 1979, Chapter 21, pp. 355-381.
12. Piscator, M. Cadmium—exposure and effects in the general population and in occupationally exposed workers. In: *Clinical, Biochemical, and Nutritional Aspects of Trace Elements*. (A. S. Pra-

- sad, Ed.), Alan R. Liss, Inc., New York, 1982, pp. 521-536.
13. Sharrett, A. R., Carter, A. P., Orheim, R. M., and Feinleib, M. Daily intake of lead, cadmium, copper, and zinc from drinking water: the Seattle study of trace metal exposure. *Environ. Res.* 28: 456-475 (1982).
 14. Gutenmann, W. H., Bache, C. A., and Lisk, D. J. Cadmium and nickel in smoke of cigarettes prepared from tobacco cultured on municipal sludge-amended soil. *J. Toxicol. Environ. Health* 10: 423-431 (1982).
 15. Elinder, C. G., Kjellström, T., Lind, B., Linnman, L., Piscator, M., and Sundstedt, K. Cadmium exposure from smoking cigarettes: variations with time and country where purchased. *Environ. Res.* 32: 220-227 (1983).
 16. Scherer, G., and Barkemeyer, H. Cadmium concentrations in tobacco and tobacco smoke. *Ecotoxicol. Environ. Safety* 7: 71-78 (1983).
 17. Buchet, J. P., Lauwerys, R., Vandevorde, A., and Pycke, J. M. Oral daily intake of cadmium, lead, manganese, copper, chromium, mercury, calcium, zinc and arsenic in Belgium: a duplicate meal study. *Food Chem. Toxicol.* 21: 19-24 (1983).
 18. Guthrie, B. E., and Robinson, M. F. Daily intake of manganese, copper, zinc and cadmium by New Zealand women. *Brit. J. Nutr.* 38: 55-63 (1977).
 19. Schutz, A. Cadmium and lead. *Scand. J. Gastroenterol.* 14 (Suppl. 52): 223-231 (1979).
 20. Iwao, S. Cadmium, lead, copper and zinc in food, feces and organs of humans. Interrelationships in food and feces and interactions in the liver and the renal cortex. *Keio J. Med.* 26: 63-78 (1977).
 21. Tati, M., Katagiri, Y., and Kawai, M. Urinary and fecal excretion of cadmium in normal Japanese: An approach to non-toxic levels of cadmium. In: *Effects and Dose-Response Relationships of Toxic Metals* (G. F. Nordberg, Ed.), Elsevier Scientific, Amsterdam, 1976, pp. 331-342.
 22. Kjellström, T., Borg, K., and Lind, B. Cadmium in feces as an estimator of daily cadmium intake in Sweden. *Environ. Res.* 15: 242-251 (1978).
 23. Kowal, N. E., Johnson, D. E., Kraemer, D. F., and Pahren, H. R. Normal levels of cadmium in diet, urine, blood, and tissues of inhabitants of the United States. *J. Toxicol. Environ. Health* 5: 995-1014 (1979).
 24. Sharma, R. P., Kjellström, T., and McKenzie, J. M. Cadmium in blood and urine among smokers and non-smokers with high cadmium intake via food. *Toxicology* 29: 163-171 (1983).
 25. Shaikh, Z. A., and Smith, J. C. Metabolism of orally ingested cadmium in humans. In: *Mechanisms of Toxicity and Hazard Evaluation* (B. Holmstedt, R. Lauwerys, M. Mercier, and M. Robberfroid, Eds.), Elsevier/North Holland Biomedical Press, Amsterdam, 1980, pp. 569-574.
 26. Flanagan, P. R., McLellan, J. S., Haist, J., Cherian, G. M., Chamberlain, M. J., and Valberg, L. S. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology* 74: 841-846 (1978).
 27. Rahola, T., Aaran, R. K., and Miettinen, J. K. Retention and elimination of ^{115m}Cd in man. In: *Health Physics Problems of Internal Contamination*, Vol. 74 (E. Bujdosa, Ed.) Akademiai Kiado, Budapest, 1973, pp. 213-218.
 28. Newton, D., Johnson, P., Lally, A. E., Pentreath, R. J., and Swift, D. J. The uptake by man of cadmium ingested in crab meat. *Human Toxicol.* 3: 23-28 (1984).
 29. Nordberg, M. General aspects of cadmium. Transport, uptake and metabolism by the kidney. *Environ. Health Perspect.* 54: 13-20 (1984).
 30. Kjellström, T. Exposure and accumulation of cadmium in populations from Japan, the United States and Sweden. *Environ. Health Perspect.* 28: 169-197 (1979).
 31. Friberg, L., and Vahter, M. Assessment of exposure to lead and cadmium through biological monitoring: results of a UNEP/WHO global study. *Environ. Res.* 30: 95-128 (1983).
 32. Jawaid, M., Lind, B., and Elinder, C. G. Determination of cadmium in urine by extraction and flameless atomic-absorption spectrophotometry. *Talanta* 30: 509-513 (1983).
 33. Elinder, C. G., Jönsson, L., Piscator, M., and Rahnster, B. Histopathological changes in relation to cadmium concentration in horse kidneys. *Environ. Res.* 26: 1-21 (1981).
 34. Bjorland, J., and Norheim, G. Renal cadmium and zinc concentrations in horses in Norway. *Nord. Vet.-Med.* 33: 530-534 (1981).
 35. Teilmann, A. M., and Hansen, J. C. Cadmium and selenium levels in kidneys from Danish horses. *Nord. Vet.-Med.* 36: 49-56 (1984).
 36. Holm, J. Lead and cadmium levels in meat and organ samples from horses: their possible effect on the health of the consumer. *Fleischwirtschaft* 59: 737-739 (1979).
 37. Gunson, D. E., Kowalczyk, D. F., Shoop, C. R., and Ramberg, C. F. Environmental zinc and cadmium pollution associated with generalized osteochondrosis, osteoporosis, and nephrocalcinosis in horses. *J. Am. Vet. Med. Assoc.* 180: 295-299 (1982).
 38. Penumathy, L., Oehme, F. W., and Hayes, R. H. Lead, cadmium, and mercury tissue residues in healthy swine, cattle, dogs, and horses from the Midwestern United States. *Arch. Environ. Contam. Toxicol.* 9: 193-206 (1980).
 39. Elinder, C.-G., Lind, B., Piscator, M., Sundstedt, K., and Åkerberg, S. An extraction procedure may not be feasible for cadmium analysis of tissues, such as horse kidney cortex, having a very high cadmium content. *Bull. Environ. Contam. Toxicol.* 27: 810-815 (1981).
 40. Piscator, M. Long-term observations on tubular and glomerular function in cadmium-exposed persons. *Environ. Health Perspect.* 54: 175-179 (1984).
 41. Bernard, A. M., Moreau, D., and Lauwerys, R. Comparison of retinol-binding protein and β_2 -microglobulin determination in urine for the early detection of tubular proteinuria. *Clin. Chim. Acta* 126: 1-7 (1982).
 42. Roels, H., Lauwerys, R., and Dardenne, A. N. The critical level of cadmium in human renal cortex: a reevaluation. *Toxicology Letters* 15: 357-360 (1983).
 43. Nogawa, K., and Ishizaki, A. A comparison between cadmium in rice and renal effects among inhabitants of the Jinzu River Basin. *Environ. Res.* 18: 410-420 (1979).
 44. Elinder, C.-G., Piscator, M., and Linnman, L. Cadmium and zinc relationships in kidney cortex, liver and pancreas. *Environ. Res.* 13: 432-440 (1977).
 45. Tjell, J. C., Christensen, T. H., and Bro-Rasmussen, F. Cadmium in soil and terrestrial biota, with emphasis on the Danish situation. *Ecotoxicol. Environ. Safety* 7: 122-140 (1983).
 46. Davis, R. D. Cadmium—a complex environmental problem, Part II. Cadmium in sludges used as fertilizer. *Experientia* 40: 117-126 (1984).