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IN VIVO MEASUREMENT OF CADMIUM IN AN OCCUPATIONALLY-EXPOSED POPULATION

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ABSTRACT

Exposure to cadmium is recognized as a potentially serious health problem. A number of clinical abnormalities have been observed in workers occupationally exposed to cadmium. Therefore, it is essential that accurate data on body burdens be available in order to formulate dose-response relationships in man. This report describes the present Brookhaven facility for in vivo measurements of cadmium in man and recent results from a field study to a cadmium production plant.

The cadmium content of the left kidney and concentration in the liver were measured by prompt-gamma neutron activation analysis in 82 occupationally exposed workers and 10 control subjects. Organ content ranged up to 57 mg in the kidney and up to 120 ppm in the liver for the industrial group. By contrast, the values for the control group ranged from 0.4 to 11.8 mg for the kidney and 0.7 to 7.9 ppm for the liver. The geometric means were 3.7 mg for the kidney and 2.7 ppm for the liver in the control group. When the data were analyzed to provide an estimate of the 'critical' concentration for the kidney, a range of 300-400 μg/g for the renal cortex was calculated. These results are compared with the available data in the literature.

DISCLAIMER

INTRODUCTION

The exposure of man to cadmium is recognized as a potentially serious health problem. Both short- and long-term effects of occupational exposure to cadmium have been observed for many years (1-3). Cadmium has been suggested as a possible causitive agent of emphysema, osteomalacia, anaemia, kidney dysfunction and lung carcinoma (1-4). The total accumulation of cadmium in man is dependent on the level of exposure and biological half-life in the body. Once absorbed, the metal is non-uniformly distributed, concentrating primarily in the kidneys and liver. In a normal subject, the kidneys retain the largest absolute amount and also have the highest concentration.

Previously, data on the body burden of cadmium in man has been derived primarily from autopsy studies. The recent development of *in vivo* measurement techniques (5-8), however, has made it possible to evaluate the status of the active worker. The present report, therefore, describes the continuing improvement of a mobile facility used for the *in vivo* measurement of kidney and liver cadmium. Preliminary results from a recent field study involving occupationally-exposed workers at a cadmium production plant are also included.

INSTRUMENT AND METHODS

In vivo measurements of small quantities of cadmium in man can be performed by prompt-gamma neutron activation analysis (PGNAA). A detailed discussion of the basic physics of PGNAA can be found in previous publications (5,7). This paper describes modifications and improvements of the original instrument reported at the 1977 Conference (9). These changes include (1) improved shielding, (2) Fe collimator, (3) two 24% Ge(Li) detectors, and (4) reduced organ to detector distance.

A cross-sectional view of the present instrument is shown in Fig. 1. The 78Ci ^{238}PuBe neutron source (2.2×10^8 n/sec) is housed in a 1m x 1m x 0.6m shield constructed mainly of polyethylene bricks doped with Pb and B. An additional 10 cm of Pb covers the shield, except for the area directly below the Ge(Li) detectors which has a 10 cm layer of polyethylene (Pb,B doped) and a 10 cm layer of Bi. No gamma shielding was provided above or to the sides of the detectors which were at the level of the bed. A 1.8 cm thick cap of paraffin (^{6}LiF doped) covered the detectors as an added shield against thermal neutron capture in the detectors.

The collimator opening at the top of the shield was 10 cm x 16 cm and the PuBe source was 59.2 cm below the bed. A 5.1 cm layer of Fe surrounds the source and lines the walls of the collimator. Iron was found to be the best choice of materials for reducing the mean energy of the neutrons by inelastic scattering and therefore increased the probability of capture in the polyethylene shield. The detection system consists of two 24% Ge(Li) detectors positioned approximately 18 cm from the center of the collimator. The signals from the detectors are amplified, passed through an ADC, and stored on magnetic tape for subsequent analysis of the energy region containing the 559keV gamma-ray peak from cadmium.

It is obviously important not only to accurately locate the kidney or liver within the neutron beam (see Fig. 1) but to also have information on its depth within the body. These parameters are vital since the composite sensitivity of the measurement (defined as counts/mg/rem) is dependent on (1) thermal flux distribution within the body, and (2) attenuation of the prompt 559keV gammas.

A series of measurements, therefore, were performed to evaluate the effects of body size on the composite sensitivity of the present instrument.

The calibration curves for different kidney positions are shown in Fig. 2. The posterior depth of the kidney is defined as the z-axis and the lateral depth as the x-axis. As can be seen from Fig. 2, the relative sensitivity for a heavier subject is considerably reduced when compared with a leaner subject. For example, the relative sensitivity at x = 8 cm and z = 6 cm is approximately one-half the value at x = 5 cm and z = 4 cm. These two possibilities are representative of a heavier and average sized subject, respectively. Hence it becomes quite evident that an essential requirement for accurate in vivo measurements of body stores of cadmium is to know the location of the target organ within the body. Therefore, an ultrasonic scan of the lower abdomen is employed to locate the liver and left kidney and to assist in positioning the subject properly in the neutron beam.

The levels of cadmium in the liver are expressed as ppm, as the cross-sectional area of the beam is less than the cross-sectional area of the liver. As the kidney fits within the dimensions of the neutron beam, the total amount of cadmium (in mg) in the kidney is obtained. The dose rate (neutrons and gammas) at the level of the bed is $\sim$0.85 rem/hr (quality factor = 10). The sensitivity of the facility is 444 counts/mg/rem for cadmium in the kidney and 269 counts/mg/rem for cadmium in the liver of an Alderson phantom. For a maximum measurement time of 2000 sec, the dose is $\sim$0.5 rem with a cadmium detection limit (2 SD above background) of 2.2 mg for the kidney and 1.5 µg/g for the liver.

The Alderson phantom was used to determine the interference between the kidneys and liver. The original BNL system was found to have minimum cross-interferences (9). The present facility, however, had cross-interferences between the two organs. The major contributions were: (1) 21% interference from the liver to the left kidney; (2) 9% interference from the right kidney to the left kidney; and (3) 24% interference from both kidneys to the liver. The net counts in each worker's in vivo measurements were adjusted for these contributions. Further investigations have indicated that these cross-interferences were attributable, in part, to the absence of shielding to the sides and above the detectors and to the shorter distance between the organ and detectors.

RESULTS AND DISCUSSION

The first field study involved the in vivo measurement of kidney and liver cadmium in 92 adult males. The industrially exposed group consisted of 82 employees ranging in age from 18 yrs to 85 yrs and work histories from 6 weeks to 45 years. The relationship between kidney cadmium (mg) and liver concentration (ppm) for the industrial workers is shown in Fig. 3. The data points are grouped according to years of employment. The kidney data ranged from 0.9 mg to 57 mg, while liver concentrations ranged from 0.8 ppm to 120 ppm. The seven workers with kidney cadmium levels above 40 mg had been employed at the plant more than 10 years. Forty-two percent (35 workers) had kidney cadmium values greater than 20 mg. No retired workers or active laborer with more than 20 years of employment had a kidney content above 35 mg. The majority of these workers had kidney cadmium values in the 20-30 mg range except for those with liver concentrations above 60 ppm. In general, the kidney content increased with increasing liver concentration until approximately 40 ppm is reached in the liver. As the liver concentration continues to increase further, the kidney cadmium level shows a decrease.

The bi-phasic response between kidney and liver Cd is described by the dashed line in Fig. 3 which is based on a two-component linear model fit to the data. The kidney cadmium value at the 'breakpoint' is 31±9 mg; the associated liver concentration is approximately 35 ppm.

It was difficult to identify an individual worker with any one specific operation at the plant since the limited work force required rotation of the workers among different operations on a routine basis. The total work force, however, was divided into three major categories: laborers (40 active, 21 retired), office workers (8 active, 4 retired), and miscellaneous workers (3 active, 6 retired). The laborers worked in areas of the plant directly involved in the processing of cadmium. The office employees (accountants, clerks, chemist, and management personnel) and miscellaneous workers (machinists, mechanics, security guards, metallurgist) had limited exposures to cadmium. Most of the employees in the miscellaneous group, however, had significant prior work histories as laborers.

The kidney and liver cadmium data had a log-normal distribution, therefore, the mean values were calculated as geometric means and geometric standard deviations. The mean kidney and liver cadmium values by job classification (laborer, office, miscellaneous) and employment status (active vs retired) are given in Fig. 4. The mean kidney cadmium levels for the three occupational groups of active workers were 17.6 mg (laborers), 5.2 mg (office) and 32.4 mg (miscellaneous). The retired workers had mean kidney values of 18.6 mg (laborers), 6.9 mg (office) and 34.4 mg (miscellaneous). The associated liver concentrations were 21.8, 9.3, and 46.5 ppm for the active groups and 38.1, 5.7, and 34.4 ppm for the retired groups, respectively. By contrast, the 10 males in the control group had mean cadmium values of 3.7 mg for the kidney and 2.6 ppm for the liver. These data are in agreement with previous findings for a non-occupationally exposed population (10). In general, there is little difference in the mean kidney and liver cadmium data between the active and retired workers. However, when compared with the control group, the mean kidney and liver values for the office workers were approximately 1.5 to 3 times higher. These differences are even greater for the laborer and miscellaneous categories, ranging from 5 to 9 times higher for the kidney and 8 to 15 times higher for the liver.

The levels of kidney cadmium were also examined in terms of years of employment or retirement (Table I). The average values for laborers with less than 5 yrs employment and for office workers did not differ significantly from the values of the control group. The kidney cadmium value reached a maximum of 30.2 mg in the 5-10 year employment group and remained relatively constant thereafter. Similarly, the mean cadmium level in the liver reached a peak by 10 yrs of industrial exposure, also with insignificant variations thereafter (11).

Further comparisons were based on the kidney cadmium data and urinary levels of β_2-microglobulin. The concentration of β_2-microglobulin (low molecular protein) can be expected to increase in the urine as an early indicator of renal tubular damage. The use of urinary β_2-microglobulin (Uβ-2), therefore, has been proposed as a monitor to assess the renal status of a worker. The relationship between Uβ-2 and kidney cadmium in the present industrial population is shown in Fig. 5. The Uβ-2 data were grouped into three regions: Region I (Uβ-2<400 μg/l), Region II (400 μg/l<Uβ-2<3600 μg/l), and Region III (Uβ-2>3600 μg/l). Uβ-2 values in Region I are within the normal range although kidney cadmium values range up to 57 mg. In Region III, where the Uβ-2 values are significantly elevated above normal (presumably representing an advanced state of proteinuria), the kidney cadium values are generally below 30 mg. Twelve of the workers in Region III also had either elevated serum creatinine or elevated plasma β_2-microglobulin levels (indicates of renal glomerular damage). The 10 workers in Region II can be separated into two groups. The five workers with higher kidney cadmium values had ratios of kidney cadmium to liver concentration similar to the value for workers in Region I. The remaining five workers in Region II had low kidney cadmium values and kidney to liver ratios that would associate them with Region III. Three of these workers also had abnormally high serum creatinine

levels. We propose that the five workers in Region II with the higher kidney cadmium burdens and normal kidney/liver ratios represent an early transitional phase from Region I to Region III before significant cadmium is lost from the kidney. The five workers in Region II with low kidney/liver ratios may represent a prolonged moderate state of proteinuria without excessively elevated Uβ-2 values yet significant lost of cadmium from the kidney. It is important to note, however, that the two subgroups within Region II can be separated solely on the basis of their kidney data and value of the kidney/liver ratio. The five workers in Region II with the higher kidney values have an average kidney content near 32 mg cadmium.

An alternative method of estimating the range of kidney cadmium values associated with normal renal function was based on the kidney data for laborers in only Region I (i.e. normal Uβ-2 levels). The cumulative frequency distribution of kidney cadmium data for the laborers in Region I indicates 38 to 42 mg for the 90th to 95th percentiles. That is, 90 to 95 percent of the workers with normal kidney function (as judged by Uβ-2 levels below 400 µg/l) could be expected to have kidney cadmium burdens below 38 to 42 mg (11). This range, therefore, may be regarded as an upper limit for the critical level in the kidney.

CONCLUSIONS

The accumulation of cadmium in man due to industrial exposures has been determined by an *in vivo* activation technique. These data along with clinical indices of kidney dysfunction have been used to estimate the critical level of cadmium in the kidney. In all cases this critical value would appear to be greater than 30 mg. Although the cadmium content of the whole kidney was measured, the renal cortex concentration was calculated for comparison with data available in the literature (Table II). The WHO Task Group (12) reported a range of 100 to 300 µg/g for the renal cortex, based on autopsy and biopsy data from humans. Nomiyama (13), however, has pointed out that a majority of these subjects had clear evidence of proteinuria and, therefore, presumably had lost significant amounts of cadmium from the kidney. The only other *in vivo* data reported is that of Roels et al (14) where 200-250 µg/g is the estimated range. Our data would indicate 300-400 µg/g for the renal cortex and is in general agreement with the 380-470 µg/g range observed by Nomiyama et al (15).

The importance of an accurate estimate of the critical concentration for the renal cortex is more than an academic issue. For example, the standards for air quality in the work place are calculated on the basis of an allowable body burden. Also, the Swedish Government recently banned cadmium products based, in part, on the WHO recommendation of 200 µg/g as the critical value. The wide range of values presented in Table II would indicate that further studies must be made to evaluate the dose-response relationship in man. These studies should include environmental exposures of the general population and different industrial exposure conditions.

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Table I. Relationship of Kidney Cadmium with Occupation and Years of Employment or Retirement.

	Years[a]	No. of Workers (n)	Kidney Cadmium[b] (mg)	p-value, workers vs controls (p)
Controls	-	10	3.7(2.9)	
Active Workers				
Office	1-25[d]	8	5.2(1.5)	n.s.
Laborer	<1	8	5.0(1.7)	n.s.
	1-5	2	16.7(1.1)	n.s.
	5-10	2	30.2(1.2)	<.05[c]
	10-15	9	24.9(1.9)	<.05
	15-20	8	24.5(1.7)	<.05
	>20	11	23.9(1.7)	<.05
Retired Workers				
Office	1-20[d]	4	6.9(1.5)	n.s.
Laborer	<5	12	25.8(1.6)	<.02
	5-10	7	13.7(1.7)	n.s.
	>10	2	10.6(5.2)	n.s.

[a] years of employment or retirement

[b] geometric mean (geom. SD)

[c] t-test, log-normal dist.

[d] All office workers

Table II. Comparison of Different Estimates of Critical Cadmium Concentrations in Kidney Cortex

Range of Critical Concentrations of Cadmium in Kidney Cortex* (µg/g)	References and Methods of Assessment
100-300	WHO Task Group (Autopsies, biopsies; human)
200-250	Roels et al. (In Vivo Activation; human)
380-470	Nomiyama et al. (Autopsies; monkeys)
300-400	PRESENT STUDY (In Vivo Activation; human)

* Assumes kidney weight of 145gm and a cortex cadmium concentration 1.5 times that of the whole kidney.

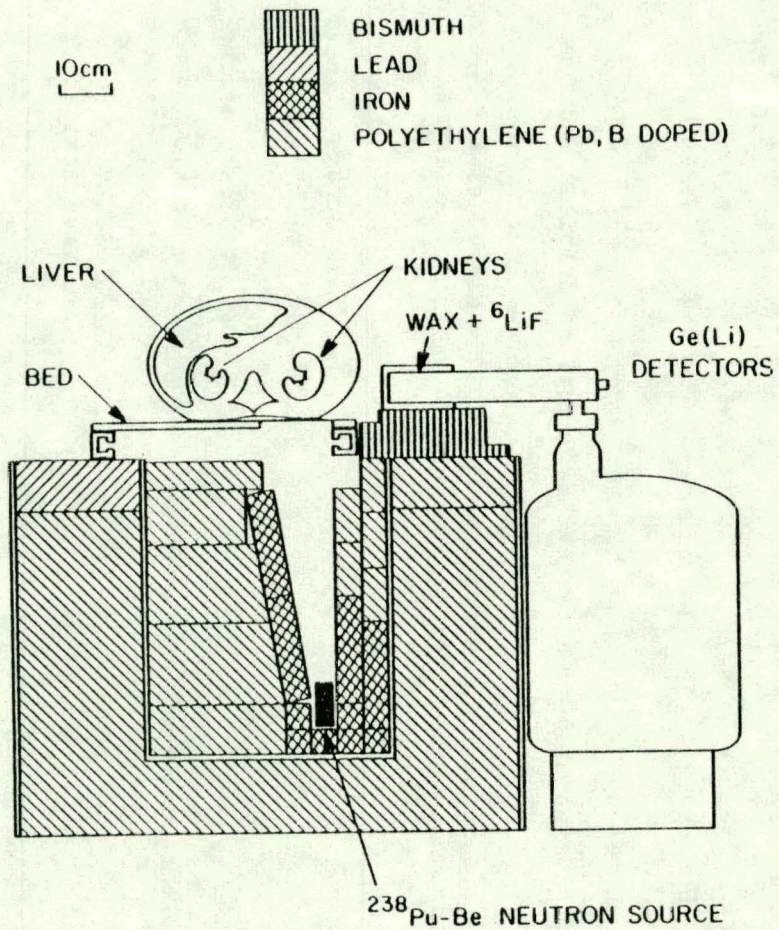

Fig. 1. Cross-Sectional View of In Vivo Measurement Facility.

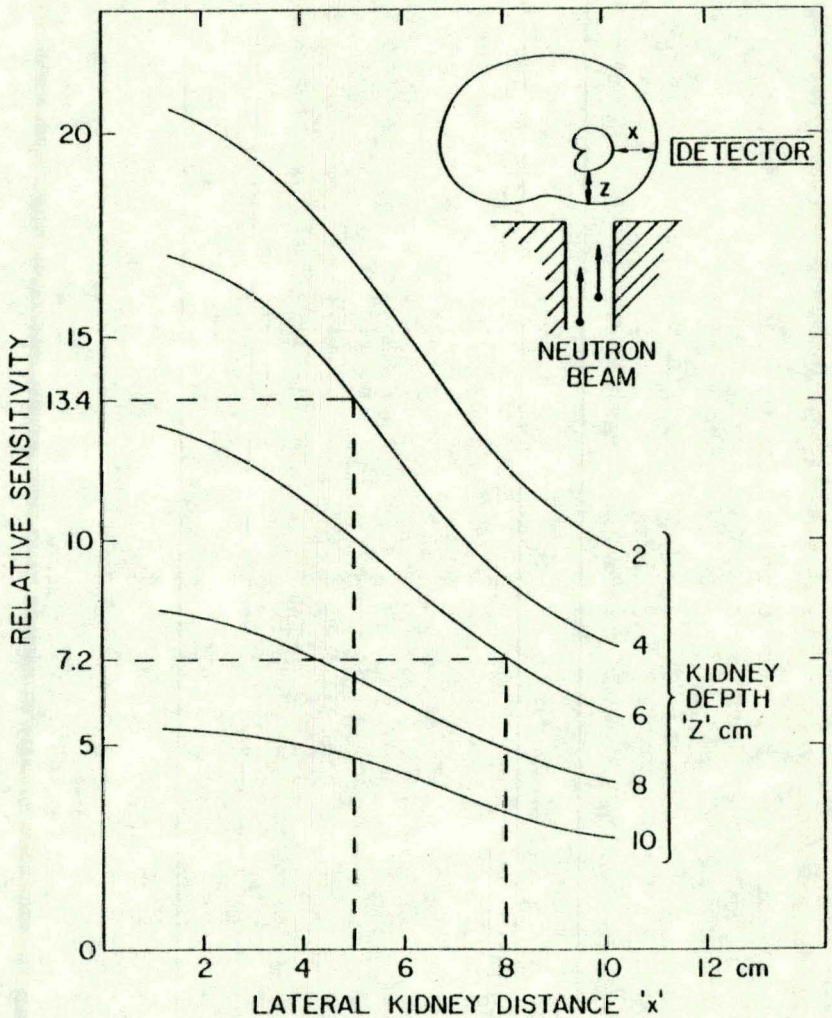

Fig. 2. System sensitivity curves for different kidney positions within the body.

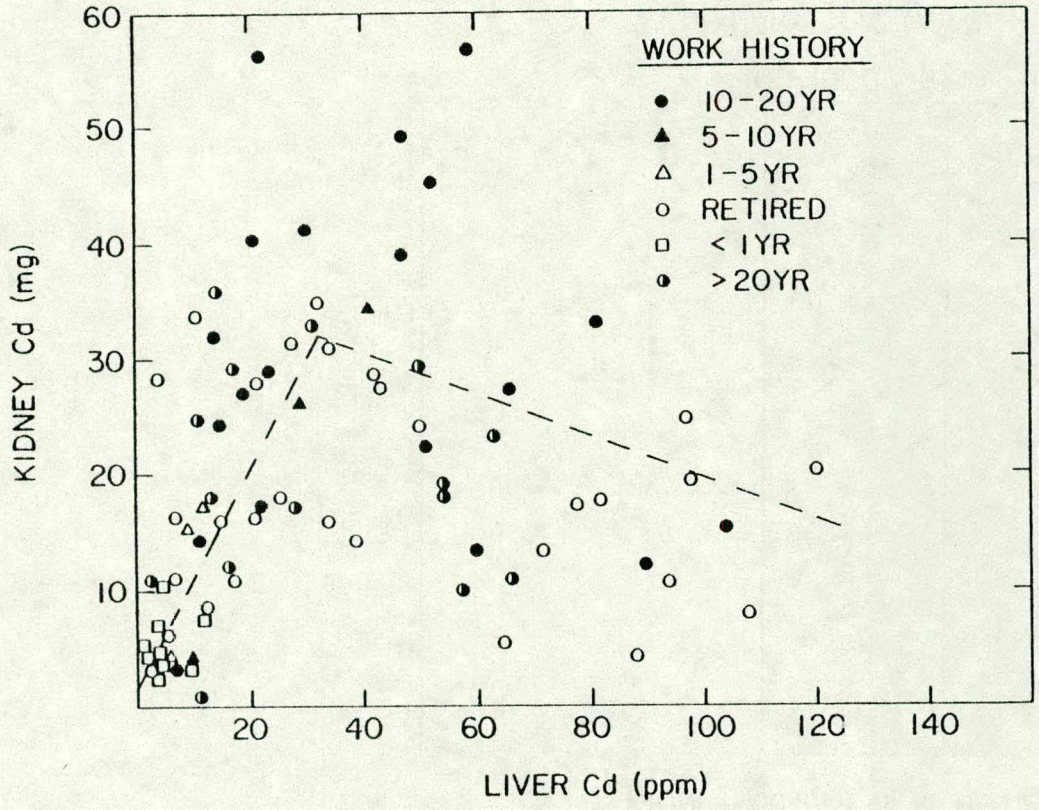

Fig. 3. Relationship between kidney Cd (mg) and liver Cd (ppm) for industrial workers. The dashed line represents a two-component model fit to the data.

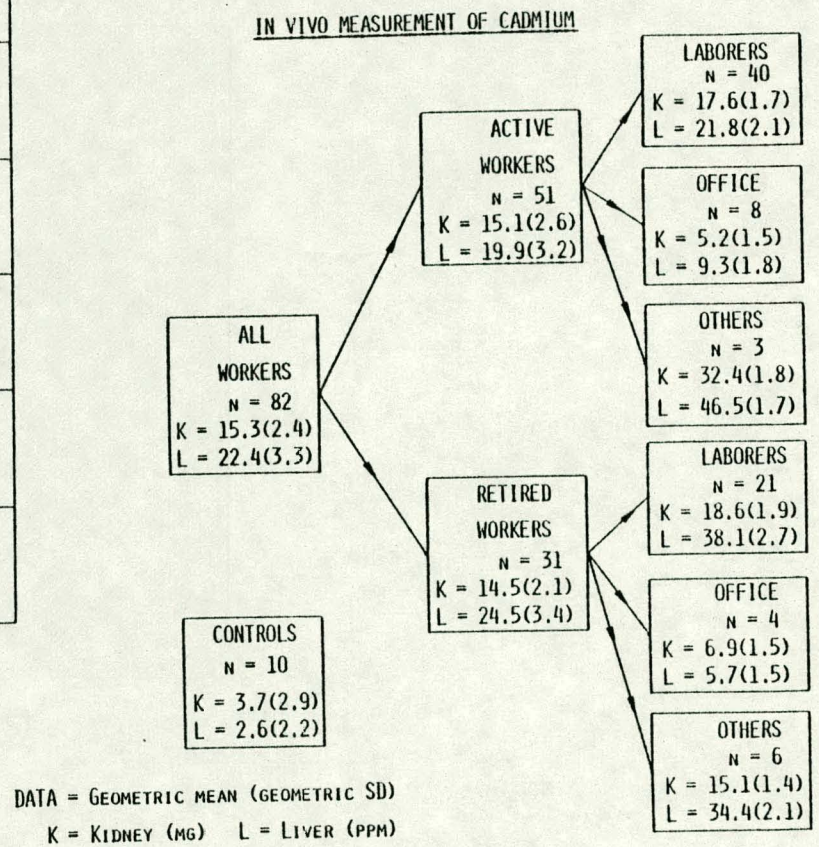

Fig. 4. Mean kidney and liver cadmium values for different occupational catagories.

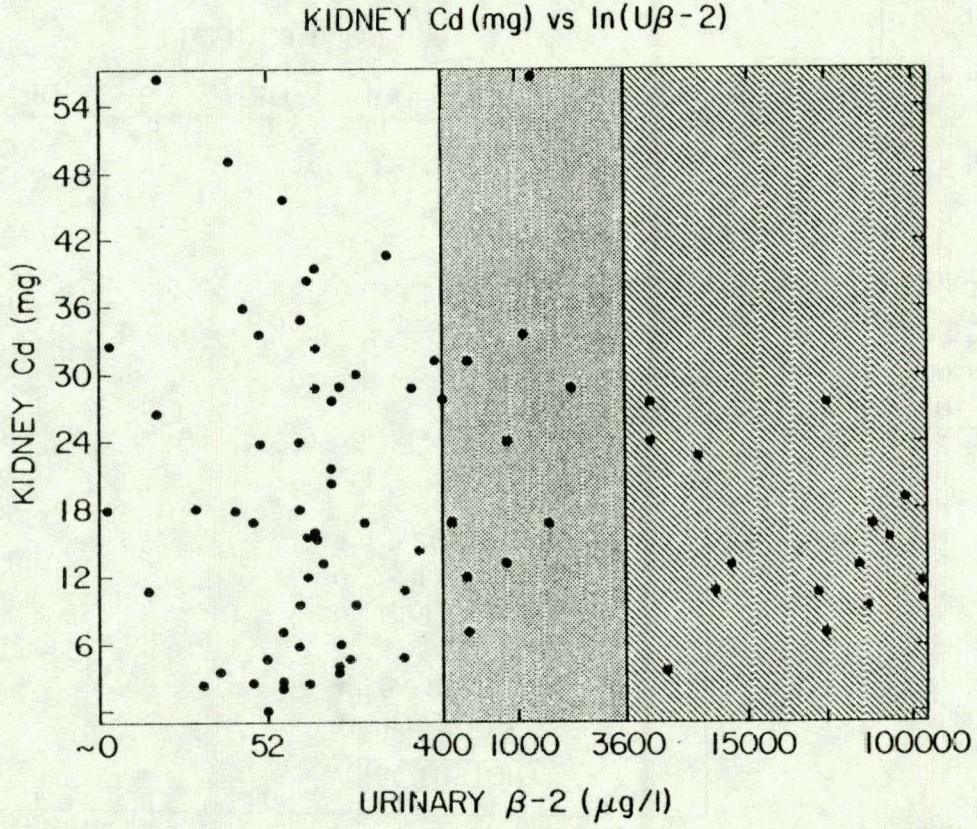

Fig. 5. Relationship between kidney Cd (mg) and urinary β_2-microglobulin (μg/l). The three regions are defined in the text.