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# CRITICAL ORGAN CONCENTRATION OF CADMIUM IN OCCUPATIONALLY-EXPOSED WORKERS

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## ABSTRACT

Excessive exposure to cadmium is recognized as a potentially serious health problem. Clinical abnormalities have been observed in a significant number of 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 provides a comparison with other portable systems. The cadmium detection limits are 2.2 mg in the kidney and 1.5 ppm in the liver for the Brookhaven system. In a recent field study, the cadmium content of the left kidney and concentration in the liver were measured 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. The corresponding cadmium concentrations in the liver and urine were 30-42 ppm (liver) and 22-28 μg/g creatinine (urine), respectively. Blood and urine levels of cadmium and $\beta_2$-microgloubin were also evaluated as possible biological indicators of organ content.


## INTRODUCTION

The toxic effects on humans of chronic industrial exposure to cadmium were first reported over 30 years ago (Friberg, 1948; Friberg, 1950). Both short- and long-term effects associated with cadmium exposure have indicated the kidneys and lungs as the major target organs of cadmium toxicity. Although cadmium has been suggested as a possible causitive agent of emphysema, osteomalacia, anaemia, and prostate cancer, the most prominent finding is a nephrotoxic effect, usually characterized by proteinuria. The kidney appears to be more sensitive to the chronic effect of cadmium than the lung both in industrially exposed workers (Friberg et al, 1974; Nordberg, 1976; Lauwerys et al, 1979a; Kazantzis, 1979)

and in the general population residing in areas of high cadmium contamination (Tsuchiya, 1978; Nogawa et al, 1979). Thus, the kidney has been identified as the critical organ in an evaluation of dose-response relationships of chronic cadmium exposures in man.

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. The cadmium burden in the kidney at which adverse effects occur has been defined as the critical level for the whole organ or the critical concentration for the renal cortex (Nordberg, 1976). In order to estimate the critical threshold value for cadmium concentrations in the renal cortex required to produce proteinuria, most studies have been based primarily on data from autopsies, (Friberg et al, 1974; WHO Task Group, 1975; CEC Task Group, 1978). The recent development of in vivo measurement techniques, however, has made it possible to evaluate the status of the active worker. The present report describes the continuing improvement of a mobile facility used for the in vivo measurement of kidney and liver cadmium and results from a recent field study involving occupationally-exposed workers at a cadmium production plant. In vivo measurements of kidney and liver cadmium were the basis for an estimation of the critical concentration in the kidney cortex required to produce significant signs of renal dysfunction.

## MATERIAL AND METHODS

### In Vivo Measurement of Cadmium

Neutron activation measurements of the subjects were made in the Brookhaven mobile facility (Ellis et al, 1980). A cross-sectional view of the instrument is shown in Fig. 1. The neutron source ($2.2 \times 10^8$ 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 two Ge(Li) detectors (24% efficiency) in order to provide added shielding against thermal neutron capture in the detectors.

The activation technique is based on the specific nuclear properties of $^{113}$Cd, a naturally-occurring stable isotope. Excited $^{114}$Cd, is produced in the neutron capture process. This isotope decays promptly ($<10^{-14}$ sec), emitting gamma rays which are detected externally to the body. Thus, the subject must be irradiated and counted simultaneously. Also, it is vitally important not only to accurately locate the kidney or liver within the neutron beam (see Fig. 1) but to also have accurate information on its depth within the body (Morgan et al, 1981). As can be seen from Fig. 2, the sensitivity for a heavier subject is considerably reduced when compared with a leaner subject. The two possibilities in Fig. 2 are representative of a heavier and average sized subject, respectively. Hence it becomes quite evident than 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 in vivo measurement is rapid and non-invasive. The maximum localized skin dose for a measurement time of 2000 sec is less than 0.5 rem (QF=10), and thus there is minimal risk to the subject. For "in-the-field" measurements, the limits of detection(2 SD above background) are 2.2 mg for the kidney and 1.5 µg/g for the liver. A comparison of the detection limits with other portable facilities is given in Table 1. An in-depth discussion of these differences has been presented elsewhere (Morgan et al 1981b). The Brookhaven system has the lowest detection limits which are well within the range of 'normal' values for the kidney and liver.

Study Population

The populations examined consisted of a group of 83 adult male workers employed in a cadmium production plant and a control group of 10 adult males with no known industrial cadmium exposure. 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.

For an evaluation of renal function, a series of laboratory tests were performed. Included were measurements of blood and urine for $\beta_2$-microglobulin (Phadebas $\beta_2$-microglobulin test, Pharmacia, Uppsala, Sweden), creatinine, total protein, and cadmium. Subsequent to the initial study, plasma and urine metallothionein levels were assayed for approximately 60 workers (Tohyama et al, 1981).

RESULTS

The relationship between kidney cadmium (mg) and liver concentration (ppm) for the industrial workers and the control group is shown in Fig. 3. The kidney and liver cadmium data have a log-normal distribution. In the occupationally exposed group, 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. In general, retired workers or active laborers with more than 20 years of employment had a kidney cadmium level below 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. The bi-phasic response between kidney and liver Cd has been described by a two-component linear model fit to the data (Ellis et al, 1981). The kidney cadmium value at the 'breakpoint' is 31 $\pm$ 9 mg; the associated liver concentration is approximately 35 ppm.

Since duration of employment may provide an approximate cumultive index of exposure (Lauwerys et al, 1979a), the levels of kidney and liver cadmium were also examined in terms of years of employment and retirement. The average values for active office workers (employment ranged from 1 to 20 years) and laborers with less than five years of employment at the plant did not differ significantly from the values of the control group. The mean value of cadmium in the kidney reached a peak value of 30.2 mg within a period of 5 to 10 years of employment for the laborers, and remained relatively constant thereafter. The mean cadmium level in the liver for active laborers also reached a peak value ($\sim$40 ppm) by fifteen years of industrial exposure. Individual values, however, varied from 10 ppm to 110ppm in this group.

An alternative approach to the determination of the critical concentration for the kidney can be based on an evaluation of urine and blood levels of $\beta_2$-microglobulin, creatinine, protein, and cadmium. Since elevated levels of $\beta_2$-microglobulin in urine have been observed when chronic cadmium exposure has occurred, its use as an early indicator of renal tubular damage has been proposed. The distribution of workers when grouped according to their kidney function (urinary $\beta_2$-microglobulin >400 µg/l or serum creatinine >1.4 mg/100 ml were considered abnormal) is shown in Fig. 4. The criteria for normal kidney function may alternately be defined in terms of the proteinuria and $\beta_2$-microglobulin clearance rates. Using this criteria, the cumulative frequency distribution of kidney and liver cadmium for the laborers are shown in Fig. 5. For laborers with normal renal function, the 90-95th percentiles correspond to 39-41 mg cadmium for the total kidney.

Biological Indicators

In order to evaluate the usefulness of cadmium or $\beta_2$- microglobulin levels in blood and urine for estimating organ levels of cadmium in humans, non-parametric correlation analysis were performed (SPSS, N.H. Norman, Editor, McGraw-Hill, 1975). The results are given in Table 2. Urinary $\beta_2$-microglobulin levels were not statistically correlated with organ content. Both blood and urine cadmium levels were statistically correlated. Repeated measurements of blood and urine cadmium, however, revealed substantial fluctations within an individual, possibly reflecting changes in exposure conditions. It does appear that a relationship between urinary excretion of cadmium and total body burden may exist on a group basis. Unfortunately, the wide scatter due to individual fluctations significantly reduces the predictive value on an individual basis. In the present group of active workers, the uncertainty in predicting organ content based on urinary cadmium is $\pm$ 12 mg for the kidney ($\pm$ 120 µg/g cortex)and $\pm$ 30 ppm for the liver. A preliminary analysis of urinary metallothionein as a possible biological indicator of organ content has also been performed (Tohyama et al, 1981).

DISCUSSION

A comparison of the present data with previous estimates of the critical concentration in the kidney cortex is provided in Table 3. Kidney cadmium data from humans has been quite limited due, in part, to the measurement techniques available. Autopsy data from cadmium-exposed workers have been compiled by Friberg et al (1974) and for the high environmental exposures in Japan by Tsuchiya (1978) and Friberg et al (1974). A WHO Task Group (1975) selected autopsy and biopsy data from 28 subjects and tentatively concluded that for the kidney cortex, the critical concentration is between 100 and 300 µg/g. Nomiyama (1977), however, has pointed out that 24 of these 28 subjects had either proteinuria or pathological changes in the renal cortex and, therefore, had probably lost cadmium from the kidney.

Additional evidence (Nomiyama et al. 1979) for setting a value for the critical concentration of cadmium in the kidney cortex higher than that proposed by the WHO comes from estimates of the critical value as being between 380 and 470 µg/g wet weight. More recently, Roels et al (1979) reported the critical concentration for the renal cortex to be between 200 and 250 ppm, based, in part, on the *in vivo* data of Chettle et al (1979).

In the present study, 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 for the total kidney (300-400 µg/g cortex).

CONCLUSIONS

The importance of an accurate estimate of the critical concentration for the renal cortex is more than an academic issue. The relationship between daily exposure to cadmium and the cadmium concentration in the kidneys may provide the basis for estimating acceptable exposure limits. Setting a maximum allowable average daily intake for the general population or permissible exposure levels for industrial workers is highly dependent on the value of the critical level for the kidney. The data for cadmium in this study favors a threshold limit of approximately 300 µg/g wet weight for the renal cortex. Further studies may help to assess the effects of biological variations among individuals, particularly in conjunction with factors such as age, sex, dietary habits, and general state of health. From these considerations, guidelines for acceptable levels of cadmium in food, water, and industrial air can be established in order to provide an adequate safety margin.

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Table 1. Comparison of Portable Facilities for In Vivo Measurement of Cadmium

| Laboratory | Detection Limit* | | Reference |
|---|---|---|---|
| | Kidney (mg) | Liver (ppm) | |
| Brookhaven | 2.2 | 1.5 | Ellis et al (1980) |
| Swansea | 3.3 | 2.2 | Evans et al (1979) |
| Birmingham | 4.5 | 10 | Chettle et al (1979) |
| Brisbane | 6.7 | 6.7 | Krauel et al (1980) |
| Toronto | --- | 10 | McNeill (1980)** |
| Baghdad | --- | 20 | Al-Hiti et al (1979) |

* detection limit = 2 SD above background
** private communication

Table 2. RESULTS OF NON-PARAMETRIC CORRELATION ANALYSIS*

| | KIDNEY Cd (mg) | LIVER Cd (ppm) | BODY BURDEN of Cd** (mg) |
|---|---|---|---|
| Urine Cd (µg/g creatinine) | .54[a] | .70[a] | .74[a] |
| Blood Cd (µg/100ml) | .38[b] | .65[a] | .67[a] |
| Plasma $\beta_2$ (µg/l) | .16 | .40[b] | .30[c] |
| Urine $\beta_2$ (µg/g creatinine) | .12 | .14 | .19 |

* Spearman rank-order correlation ($r_s$)
a($p<.001$) b($p<.01$) c($p<.05$)

** The kidneys and liver are assumed to represent approximately one-half total body burden

Table 3. 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) |

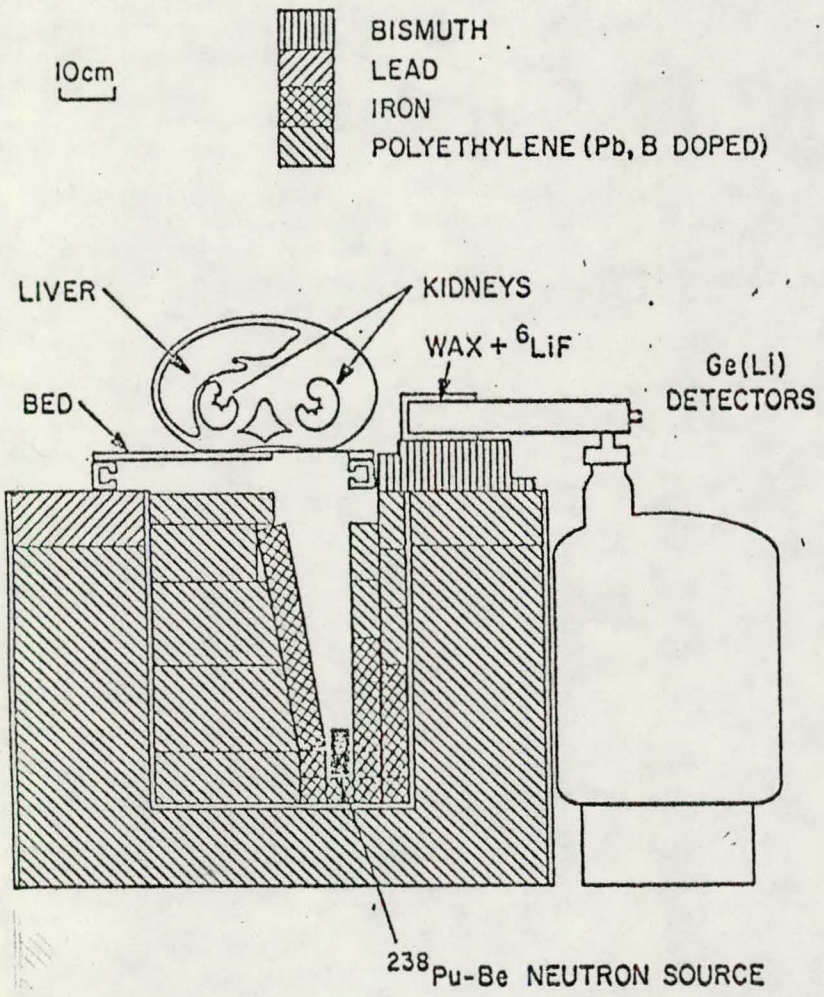


Fig. 1. Cross-Sectional View of In Vivo Measurement Facility.

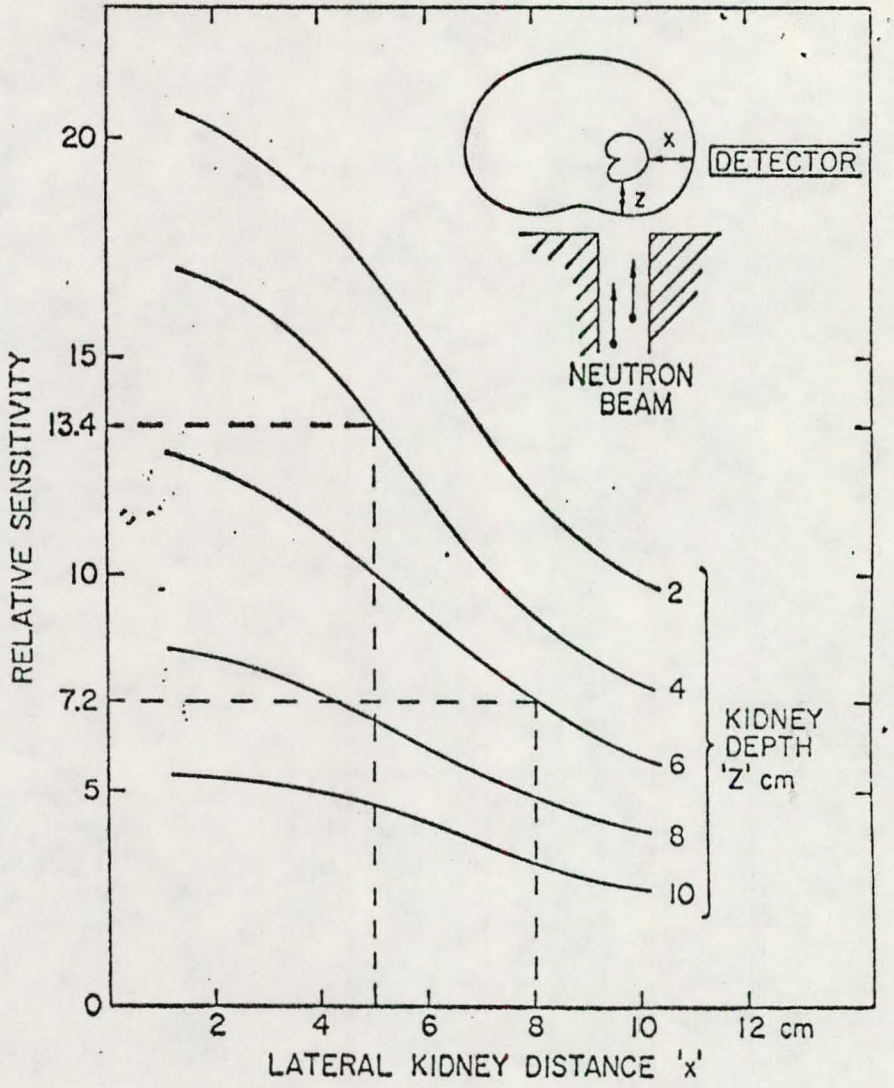


Fig. 2. System sensitivity curves for different kidney positions within the body.

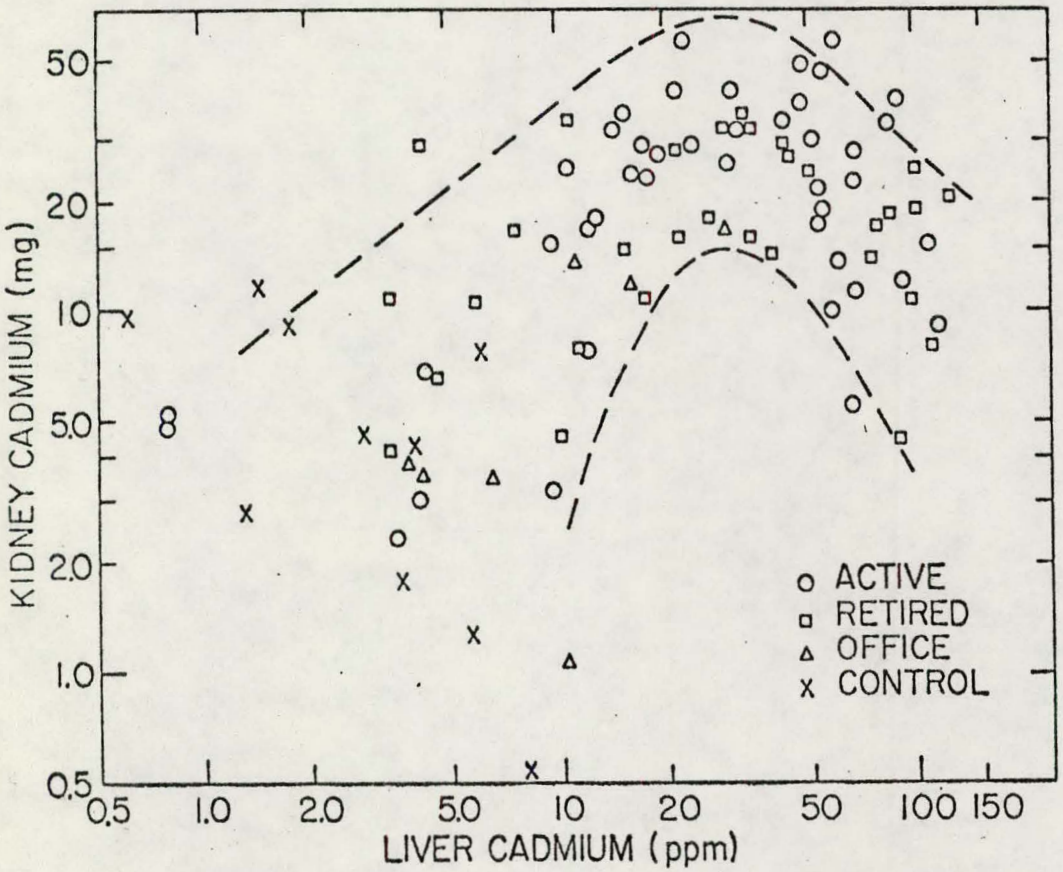


Fig. 3. Relationship between kidney Cd (mg) and liver Cd (ppm) for industrial workers and controls. The laborers were separated as active or retired workers.

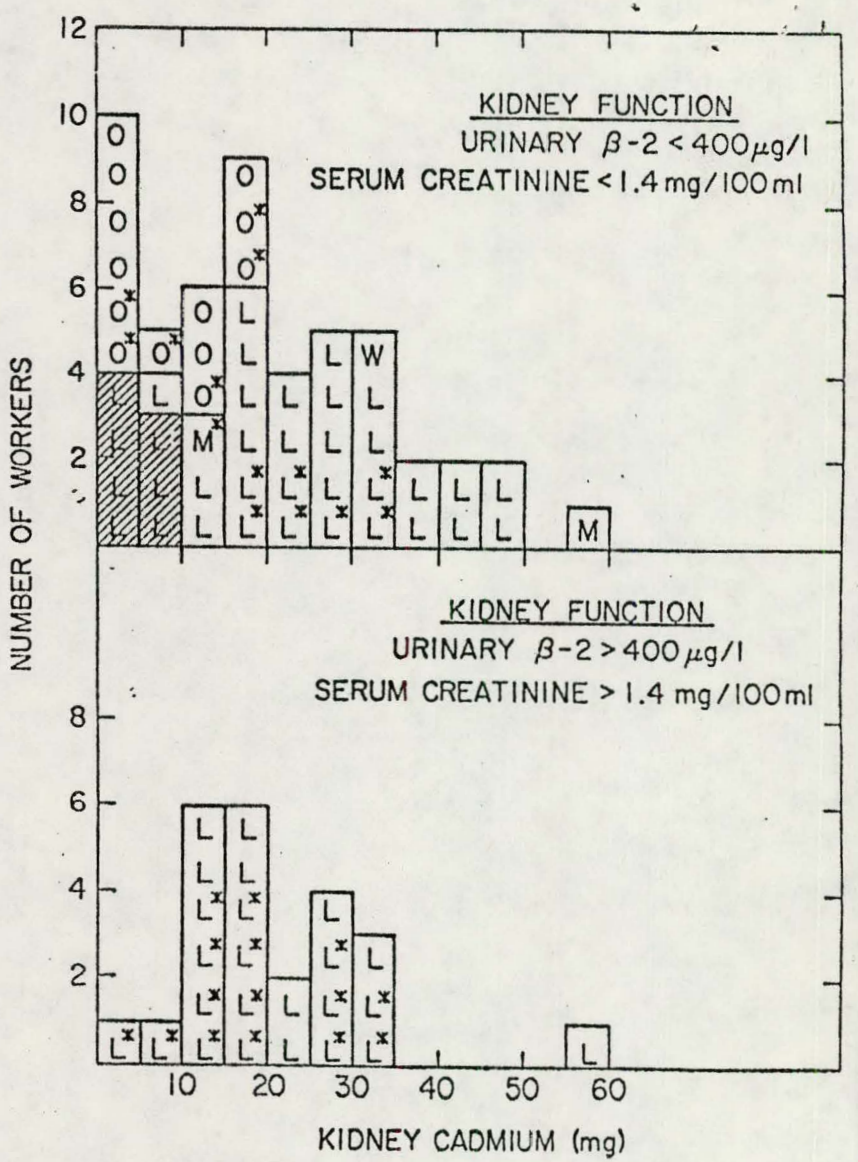


Fig. 4. Distribution of workers based on kidney function test. Shaded areas denote laborers with less than 1 year of employment. L = laborer, 0 = office, W = warehouse, M = metallurgist, * = retired worker.

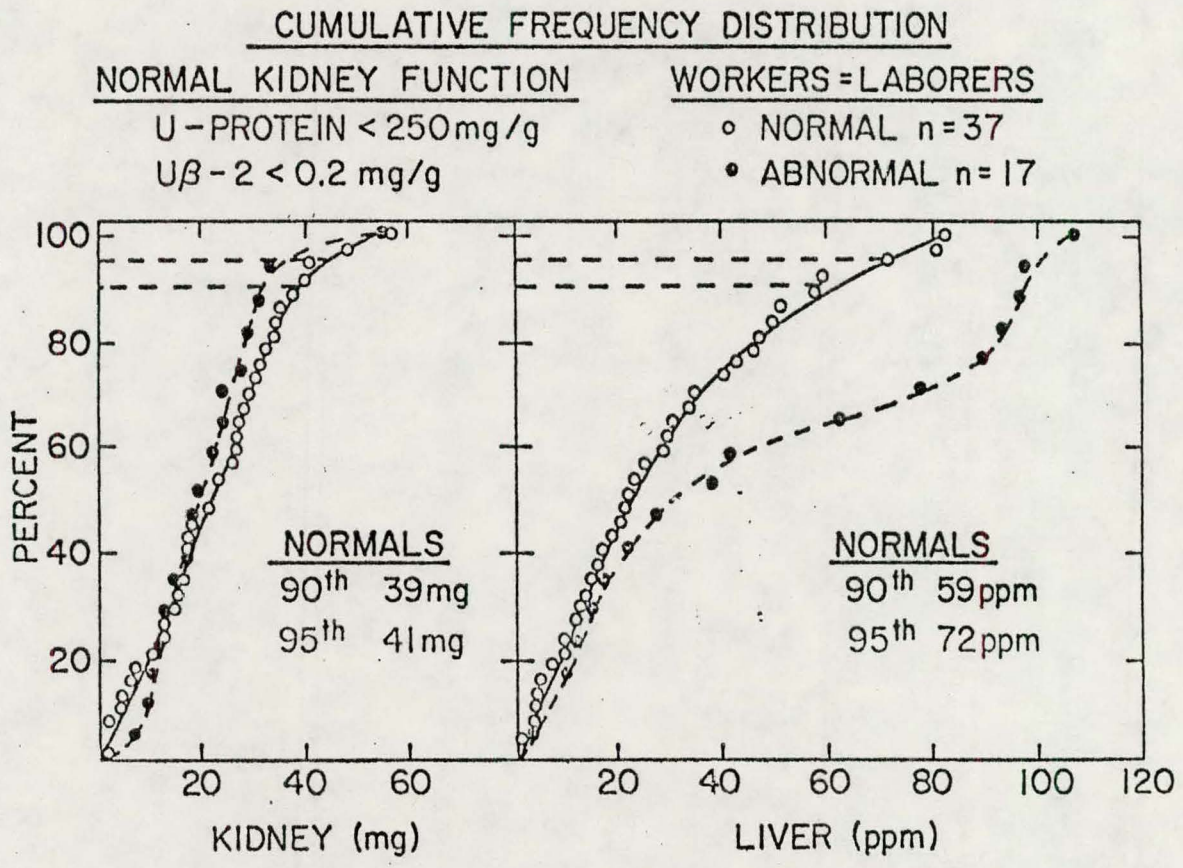


Fig. 5. Cumulative frequency distribution of kidney and liver cadmium for laborers with normal and abnormal kidney function. The criteria for normal kidney function is urinary protein <250 mg/g creatinine and urinary $\beta_2$-microglobulin <0.2 mg/g creatinine.