In vivo analysis of cadmium in battery workers versus measurements of blood, urine, and workplace air

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Abstract

Objectives—To measure in vivo the cadmium concentrations in kidney cortex (kidney-Cd) and in superficial liver tissue (liver-Cd) of nickel cadmium battery workers, and to compare the results with other commonly used estimates of cadmium exposure (current concentrations of cadmium in blood (B-Cd) and urine (U-Cd)) or repeated measurements of cadmium in workplace air (CumAir-Cd).
Methods—The study comprised 30 workers with a range of duration of exposure of 11-51 years. 13 subjects were currently employed, whereas the other 17 had a median period without occupational exposure of eight years before the measurements. The in vivo measurements were made with an x ray fluorescence technique permitting average detection limits of 30 and 3 µg cadmium per g tissue in kidney and liver, respectively.
Results—19 of 30 (63%) people had kidney-Cd and 13 of 27 (48%) had liver-Cd above the detection limits. Kidney-Cd ranged from non-detectable to 350 µg/g and liver-Cd from non-detectable to 80 µg/g. The median kidney-Cd and liver-Cd were 55 µg/g and 3 µg/g, respectively. Kidney-Cd correlated significantly with B-Cd (r_s 0.49) and U-Cd (r_s 0.70), whereas liver-Cd correlated significantly with U-Cd (r_s 0.58). Neither kidney-Cd nor liver-Cd correlated with the CumAir-Cd. The prevalence of β_2-microglobulinurea increased with increased liver-Cd.
Conclusions—Current U-Cd can be used to predict the kidney-Cd and liver-Cd measured in vivo. In vivo measurements of kidney-Cd and liver-Cd were not shown to correlate with the individual cadmium exposure estimates, obtained by integration of the cadmium concentration in workplace air. There may be several reasons for this, including uncertainties in the estimate of the individual cumulative exposures as well as in the in vivo measurements. There was a suggestion of a relation between liver-Cd and tubular proteinuria.

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Exposure to cadmium (Cd) may cause adverse health effects in humans.[1] Cadmium accumulates in liver and kidneys. The kidneys are considered to be the critical organs after long term exposure. In occupational health care as well as in epidemiological studies, the degree of cadmium concentration in the kidneys (kidney-Cd) and liver (liver-Cd) is estimated indirectly, with the current cadmium concentration in blood (B-Cd) or urine (U-Cd), or the time integrated cadmium concentration in workplace air (CumAir-Cd). When a critical concentration in the kidney cortex has been reached, renal damage may evolve. In such situations, the cadmium content in the kidneys decreases and is no longer accurately reflected by the U-Cd.

The ability to measure the cadmium concentration in vivo directly in the kidney and liver is attractive. Such in vivo techniques have been developed during the past decades, with either neutron activation analysis[2] or x ray fluorescence.[3] The x ray fluorescence method has a lower detection limit except for subjects with deeply situated organs. It also gives a lower mean equivalent dose to the body than neutron activation analysis.[4]

The aim of the present study was to use an x ray fluorescence method for the in vivo measurement of kidney-Cd and liver-Cd in a group of long term, occupationally exposed, subjects. In particular, our interest was to compare the results with measured concentrations of B-Cd, U-Cd, and CumAir-Cd.

Methods

SUBJECTS AND THEIR EXPOSURE

The people studied (n=30) were a subgroup of a larger group (n=900) of nickel-cadmium battery factory workers who had a duration of employment of one year or more during the years 1931 and 1992.[5] The subjects were chosen to represent workers with a wide range of past exposure to cadmium (table 1), according to the CumAir-Cd, and were not a random sample of all workers. Three participants were women. Thirteen workers were currently employed, but the other 17 had discontinued their occupational exposure between one and 31 (median eight) years before the in vivo measurements. The mean age for the 30 people was 64 (SD 7) years and the mean duration of employment of 35 (SD 13) years. Six workers of the 30 had tubular proteinuria.

In the production of nickel-cadmium batteries, cadmium was mainly in the form of oxide

Table 1 Results from in vivo measurements of kidney-Cd, liver-Cd, B-Cd, U-Cd, and U-β_2-m in occupationally exposed subjects

Subject	Age (y)	ΔT1/ΔT2 (y)	CumAir-Cd (μg/m³.y)	B-Cd (nmol/l)	U-Cd (nmol/mmol creatinine)	U-β_2-m (μg/mmol creatinine)	Kidney-Cd (SD) (μg/g)	MDC kidney (μg/g)	Liver-Cd (SD) (μg/g)	MDC liver (μg/g)
1	64	41/3	2400	70	6.8	1.9	355 (60)*	53	2 (2)	5
2	59	21/0	17800	25	4.6	15.6	181 (31)*	25	11 (1)*	3
3	50	25/0	3300	35	3.3	2.0	161 (24)*	10	6 (1)*	3
4	63	15/4	6700	60	10.4	12.4	139 (26)*	30	13 (1)*	3
5	69	11/31	800	25	3.4	130	128 (35)*	55	22 (1)*	3
6	63	45/0	4100	70	4.7	23.1	125 (20)*	13	7 (1)*	3
7	61	42/0	700	15	2.3	0.3	111 (24)*	40	0 (1)	3
8	64	38/11	2200	35	3.1	26.8	101 (15)*	6	34 (1)*	3
9	63	51/0	2600	40	5.2	16.2	96 (28)*	47	2 (1)	3
10	66	31/1	100	60	4.4	9.4	87 (20)*	30	0 (1)	3
11	51	19/0	2100	45	4.9	8.0	77 (12)*	8	13 (1)*	3
12	63	46/0	2400	—†	—†	—†	68 (2)*	35	9 (1)*	3
13	74	43/10	900	100	10.8	780	63 (11)*	13	83 (3)*	6
14§	59	41/0	1000	40	4.7	23.6	61 (29)*	52	—‡	
15	69	19/24	900	50	4.6	3600	55 (13)*	19	8 (1)*	3
16	69	13/7	1800	15	2.1	6.3	54 (11)*	15	2 (1)	3
17	63	44/0	1500	45	3.2	8.9	45 (8)*	6	3 (1)	4
18	66	48/1	1700	35	5.8	268	34 (21)	44	13 (1)*	4
19	70	50/5	3700	30	1.5	5.1	30 (15)*	30	-3 (1)	4
20	71	48/7	1900	5	1.2	0.5	28 (5)*	28	-2 (1)	3
21	72	41/7	2100	40	4.0	1.6	25 (24)	49	12 (1)*	3
22	52	26/0	1700	35	2.4	5.7	24 (18)	35	2 (1)	3
23	61	17/0	800	10	1.0	6.4	14 (9)	19	4 (1)*	3
24	48	27/0	800	20	2.9	6.1	9 (7)	12	-1 (1)	3
25§	64	47/2	900	10	0.8	4.6	7 (6)	15	—‡	
26	72	44/7	700	15	2.3	0.4	4 (24)	44	2 (1)	3
27§	60	38/0	12500	10	2.3	8.5	0 (6)	13	—‡	
28	56	16/8	800	80	2.6	3.0	-3 (22)	47	-2 (1)	4
29	64	48/1	1600	5	0.5	10.6	-20 (20)	41	-3 (1)	3
30	70	41/7	1600	10	2.0	63.7	-158 (98)	155	-1 (1)	3

* The estimated cadmium concentration exceeded the MDC.
† Data not available for this person.
‡ Not measured (body burden not estimated for this person).
§ Female.
ΔT1 = the period of employment; ΔT2 = the period of non-occupational exposure just before the measurement; MDC = the minimum detectable concentration; SD in the kidney-Cd refers to counting statistics and the contribution from positional uncertainty (± 2 mm), but the SD for liver-Cd includes only the pulse statistics.

and hydroxide. Exposure to airborne dust containing these compounds, may have occurred in a large part of the production factories. Also, exposure may have occurred from cadmium contaminated cigarettes and food. Before 1946, there were no quantitative data on work conditions, but eye witnesses describe them as very dusty.[6] Cadmium in workplace air has been measured sporadically since 1946, and systematically since 1972. Based on a previous collection of these data,[6] the average exposure for all workers has been roughly estimated to be 1 mg/m³ before 1947, 300 μg/m³ in 1947–63, 50 μg/m³ in 1964–74, and 20 μg/m³ thereafter.[7] Knowing the subject's work periods, his or her individual CumAir-Cd was roughly estimated. There may be substantial differences between workers in external exposure even if our estimates indicate the same cadmium exposure level. Also, there are certainly important differences between people in uptake of cadmium, related to smoking habits, personal hygiene, work load, and the use of personal protective equipment.

However, recently it has been possible to perform a more detailed historical exposure analysis, accounting for major differences not only between periods, but also between jobs. Historical information on the development of production, work practices, and preventive measures, was collected by means of interviews and data on protocol, and the exposure estimates (three levels) were based on all available data (Bellander et al, unpublished data). This updated information on CumAir-Cd was used in the present paper. A similar construction of a cumulative B-Cd index over a worker's work period was impossible due to lack of B-Cd measurements for long periods.

BLOOD AND URINE SAMPLES
With atomic absorption spectrophotometry blood samples and urine samples were analysed for cadmium: urine samples were also analysed for β_2-microglobulin (U-β_2-m) with a radioimmunoassay technique.[5] The B-Cd analyses were made by an external laboratory. To prevent the degradation of U-β_2-m occurring in acidic urine each worker had 4 g of sodium bicarbonate dissolved in water the night before the morning urine was collected for protein analyses.

A cut off value of 25 μg/mmol creatinine for the excretion of U-β_2-m was chosen. This value corresponds to the 90th percentile in a United States reference population.[5] Most likely the cut off level in a general population is higher than an industrially exposed group of workers as a healthy worker effect may be present in industry. Recent studies of workers exposed to mercury and controls have thus shown 95 percentiles for U-β_2-m as low as 17-18 μg/mM.[5][8]

IN VIVO MEASUREMENTS OF CADMIUM IN KIDNEY AND LIVER
The original technique for in vivo measurement of cadmium with x ray fluorescence[9] has been improved during the past 20 years by the use of partly plane polarised photons, a variable detector collimator, and a silicon detector.[10-12] The method is based on excitation of cadmium atoms by photons from modified x ray therapy equipment.

The minimum detectable concentration (MDC) is analogous to the definition of the minimum detectable amount of low level radioactivity defined in the International Commission on Radiological Units and Measurement (ICRU).[13]

$$MDC = 3 \times (N_{Bg})^{1/2} \times (C/N_{net}) \ [\mu g/g]$$

where N_{Bg} denotes the number of background counts under the characteristic cadmium x rays, N_{net} the net counts in the cadmium peaks, and C the cadmium concentration. Rearranging this equation shows that when the cadmium concentration C is equal to MDC the N_{net} is equal to three times the SD in the number of background counts (N_{Bg}). As the C and N_{net} are directly proportional to each other the MDC cannot take on a negative value. However, at low cadmium concentrations and large background values the mathematical analysis of the measured pulse height distribution (see later) can result in negative N_{net} values. This will result in a concentration C below zero. Thus, as a result a negative cadmium concentration in a kidney or liver may be reported although the MDC is above zero.

The sensitivity decreases and, accordingly, the MDC increases rapidly with larger organ depths due to a decreased detector solid angle and an increased photon attenuation. The MDC is about 3, 11, and 34 µg/g for depths to the kidney surface of 30, 50, and 70 mm, respectively. The depth dependence also implies that the measurement is strongly depth selective — that is, the cadmium concentration in the right kidney is determined essentially within a depth of about 15 mm from the kidney surface. Thus, cadmium is almost exclusively measured in the kidney cortex.[10] There is no interference from liver-Cd when kidney-Cd is measured.

Before the in vivo measurement, the kidney position and the depth to the kidney surface from the back were measured with linear array ultrasound (Philips Sono Diagnost, 2.2 MHz B-Scan) with the subject sitting in the measurement position. The kidney position was also verified at the end of the in vivo measurement. The individual difference in the kidney depth at the ultrasound measurements before and after the in vivo measurement was 1-3 mm.

Repeated measurements of the kidney depth without subject movements between measurements imply a smaller variation (±1 mm, SD).[4] This figure is consistent with the intrinsic uncertainty of the ultrasound equipment. However, when repeated measurements of the kidney, including subject movements between measurements, were made in one subject a 2-3 mm (SD) variation in the kidney depth was found. Thus, the higher figures (2-3 mm) are a combination of the uncertainty of the ultrasound equipment, the natural movement of the kidney position at respiration and expiration (see later), as well as the movement of the human body as a whole. Furthermore, the variation of the positions of the two points on the subject's back and his or her kidney surface that are used for the depth measurement, is added. A figure of 2-3 mm variation is in agreement with earlier published data.[9]

The position of the liver was assessed similarly, and the measurement position was taken to be the periphery of the liver volume. As the liver is a large organ and has a more homogenous cadmium concentration than the kidney,[14 15] the position is not supposed to be as critical as for the kidney.

Measurements were made in the right kidney due to the assumption of its lower mobility, during respiration, compared with the left kidney. However, a study of kidney mobility shows that the two kidneys have about equal mobility (2-3 mm) during both inspiration and expiration.[16] Thus, the choice of left or right kidney should not be made from this standpoint. Instead, as the photon attenuation is not equal for different human tissues—for example, soft tissue, fat, and bone—the kidney least "hidden" behind ribs and which has the smallest depth is the one to measure (see later).

The kidney-Cd and liver-Cd were calculated by calibrations made from each subject's in vivo measurement. Calibrations used a sealed plastic model containing cadmium dissolved in water. These models were placed in a water filled model of a body trunk in positions corresponding to the in vivo measured positions of the kidney and liver.

We corrected for the fact that the in vivo measurements were made in tissues which are not water equivalent. Under the assumption that the ratio between the number of net counts and background counts would be the same at both calibration and in vivo measurement, the number of net pulses at the calibration was corrected by the ratio of the number of background counts registered at the in vivo to the calibration measurements. This means that the number of net counts at the calibration was decreased if bone was present at the in vivo measurement and increased if fat was present. The validity of the correction factor was tested by putting either an air cavity or a bone equivalent model in the path between the front of the detector collimator and the kidney model. Results showed that the correction partly decreased, but did not totally eliminate, the influence of inhomogeneity. We also tested the use of the ratio of the broad incoherent scatter peak areas in the measured pulse height distributions. However, this correction procedure was inferior to the other.

The analysis of the registered pulse height distribution used a non-linear regression technique, included in a commercially available statistical program package.[17] The model fitted to the experimental data comprised a second degree polynomial background and two Gaussian peaks. These represented the cadmium K_α peaks. The tail at the low energy side of the full energy peak was modelled by an exponential function.[18 19] The position of the Gaussian peak could vary within narrow energy limits, whereas the ratio between the net counts of the K_α peaks was fixed. The estimated sum of the peak areas was converted to a cadmium concentration.

As the non-linear regression technique had not been applied to our analysis of cadmium pulse height distributions before, we compared it with two other algorithms used earlier.[10] [20] There was no significant difference (Student's t test) between the mean number of net counts of the three algorithms when these were applied to 20 pulse height distributions from calibration measurements (40 µg/g cadmium model immersed in water). The observed variation in the number of net pulses recorded was similar and somewhat higher for all algorithms compared with the theoretically expected value, considering the number of net, total, and background counts. When the three algorithms were applied to pulse height distributions, obtained from measurements on a cadmium free model (blank), the 95% confidence interval (95% CI) of the mean number of net counts, for all methods, included zero. These results do not indicate a large advantage of using the complex regression technique; however, further improvements of the technique may be possible.

The in vitro accuracy of the x ray fluorescence method has earlier been checked by comparative atomic absorption spectrophotometry measurements.[11] The test of the in vivo precision for the present set up with a silicon detector and improved electronics was done by carrying out 10 repeated measurements in a smoker. She had a short break between each measurement during which she stood up and walked about for a few minutes, then a new kidney position measurement was made. The estimated, mean (SD) kidney-Cd was 28 (9) µg/g. The uncertainty in the repeated in vivo measurements, due to counting statistics, was estimated to be 7%, which means that the main contribution to the total coefficient of variation of 30% came from the uncertainty in the positioning of the measurement volume and from non-uniform cadmium concentration within the cortex volume. This implies that the position uncertainty is prominent. The 30% figure is consistent with ±3 mm displacement of the kidney position, which gives an uncertainty in the measured kidney-Cd of ±25%, irrespective of the measurement depth and the cadmium concentration. Thus, this figure combines with the pulse statistics to the observed coefficient of variation of 30%. For comparison, the ±25% figure would be ±15% and ±8% for a ±2 mm and ±1 mm displacement, respectively. The coefficient of variation for liver-Cd, due to counting statistics only was estimated to be 26% and 3% at liver-Cd concentrations of 5 and 50 µg/g, respectively.

The uncertainty figures for the kidney-Cd were calculated (square root of the sum of quadratic terms) from the uncertainties in the pulse statistics with the error from a ±2 mm displacement (table 1). As the liver is a large organ and is thought to have a uniform cadmium concentration, a displacement of the volume intended to be studied is replaced by another part of the liver; thus, a correction was not made in this case.

From kidney-Cd measurement, the mean absorbed dose to the kidney was about 0.7

mGy and the energy imparted 0.2 mJ.[10] [21] The absorbed dose to the irradiated skin was 7 mGy and the mean absorbed dose to the whole body (energy imparted/70 kg) was 3 µGy. From the liver-Cd measurement, the absorbed dose in the measured volume was estimated to be 3 mGy.

STATISTICAL ANALYSIS

The B-Cd, U-Cd, kidney-Cd, and liver-Cd were not normally distributed, thus, non-parametric tests (Spearman rank correlation coefficient, r_s) were used. All P values were two tailed and P values < 0.05 were considered to be significant. Stepwise multiple linear regression was performed to find the predictors for B-Cd and U-Cd. The covariates included kidney-Cd, liver-Cd, and CumAir-Cd. In the regression analysis, variables which were not normally distributed were log transformed.

Results

Table 1 shows the liver-Cd, kidney-Cd, B-Cd, and U-Cd. Values for liver-Cd and kidney-Cd below the MDC, and even below zero, are presented in the tables and figures. Negative concentrations result from fitting of pulse height distributions to the inevitable statistical variation in the number of pulses. Negative values have no significance from a biological point of view, but give the reader an honest impression of the measurement accuracy and are necessary to perform accurate calculations of various means.[22]

The kidney-Cd exceeded the individual MDC in 19 of 30 cases and liver-Cd in 13 of 27 cases. The median kidney-Cd and liver-Cd were 55 µg/g and 3 µg/g, respectively. Due to the large individual variation in the MDC for kidney-Cd, a weighted (weight: the inverse of individual kidney-Cd variance) mean was calculated for the whole group. The weighted mean was 73 µg/g. The distribution of liver MDC values was less wide (3-6 µg/g), compared with kidney MDC values (6-155 µg/g), due to the greater similarity in measured depths for liver-Cd of all subjects. The distributions of U-β_2-m, B-Cd, U-Cd, kidney-Cd, liver-Cd, and CumAir-Cd were not significantly different between active and retired workers. Thus, active and retired workers were treated as one group.

In the following analyses, subjects with β_2-microglobulinuria (excretion >25 µg/mmol creatinine) were treated separately. There were significant correlations between the U-Cd and kidney-Cd (r_s 0.70, P<0.001, fig 1), and between the B-Cd and kidney-Cd (r_s 0.49, P=0.019, fig 2). The U-Cd correlated with liver-Cd (r_s 0.58, P=0.007), whereas there was no association between current B-Cd and liver-Cd. The correlation coefficient between the kidney-Cd and liver-Cd was r_s 0.43 (P=0.06, fig 3). The weighted (weight: the inverse of the individual ratio variance) mean ratio of the kidney-Cd to liver-Cd was 7. Linear regression analyses showed that the kidney-Cd explained 44% and 39% (multiple r^2) of the observed variance in the U-Cd and B-Cd,
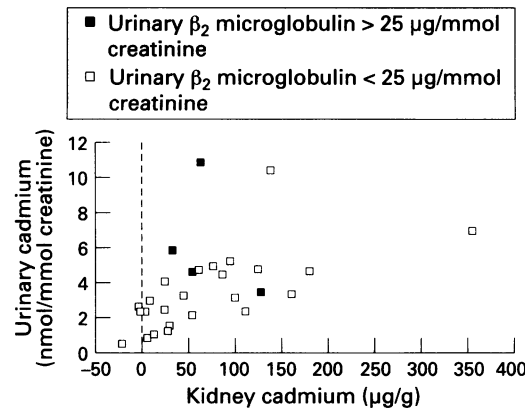
Figure 1 legend:
- Urinary β_2 microglobulin > 25 µg/mmol creatinine
- Urinary β_2 microglobulin < 25 µg/mmol creatinine

Figure 1   Cadmium concentration in urine (U-Cd) plotted against kidney cadmium concentration (kidney-Cd).

Figure 2 legend:
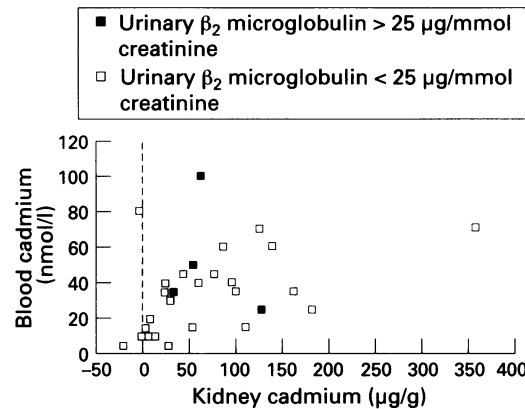- Urinary β_2 microglobulin > 25 µg/mmol creatinine
- Urinary β_2 microglobulin < 25 µg/mmol creatinine

Figure 2   Cadmium concentration in blood (B-Cd) plotted against the kidney cadmium concentration (kidney-Cd).

Figure 3 legend:
- Urinary β_2 microglobulin > 25 µg/mmol creatinine
- Urinary β_2 microglobulin < 25 µg/mmol creatinine
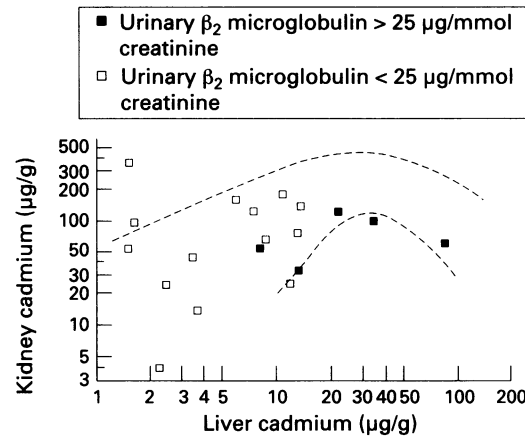
Figure 3   Kidney cadmium concentration (kidney-Cd) plotted against liver cadmium concentration (liver-Cd). The region between the curves (broken lines) shows the distribution of data points collected from other in vivo studies.[27 28 30 35] In studies where the cadmium content in the kidney was given, the content has been transformed into a cadmium concentration in the kidney cortex assuming a kidney weight of 155 g and a ratio of cadmium concentrations in cortex to the whole kidney of 1.25.

respectively. The liver-Cd and CumAir-Cd were not significant covariates.

The correlation between B-Cd and U-Cd was strong ($rs=0.81$, $P<0.001$). There was no correlation between the B-Cd, U-Cd, kidney-Cd, or liver-Cd on one hand, and the duration of employment or CumAir-Cd on the other.

When the group was divided by means of the U-β_2-m cut off level, the liver-Cd distributions were significantly different ($P=0.01$), whereas this was not the case for kidney-Cd, B-Cd, or
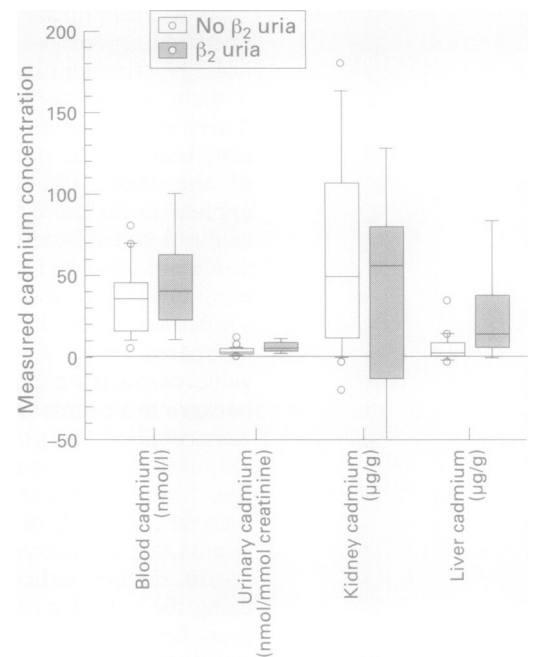

Figure 4   Box plots of B-Cd, U-Cd, kidney-Cd, and liver-Cd for the two groups of workers with increased and normal excretion of urinary β_2-microglobulin. Note that one subject's kidney-Cd value (355 µg/g) cannot be shown in the plot.

U-Cd (fig 4). Although few people were investigated in this study, a relation was indicated between liver-Cd, and response, expressed as increased excretion of U-β_2-m (table 2). No similar relation was found between kidney-Cd and response (table 2). Published data[23 24] of the kidney (one kidney; 155 g) and liver (1800 g) weights and their fraction of the body burden of cadmium (BB-Cd) were used to estimate the BB-Cd. The weighted (weight: the inverse of the individual BB-Cd variance) mean BB-Cd, estimated from the kidney-Cd and liver-Cd data separately, was 34 mg and 73 mg, respectively. When the estimation was made with the combined information of kidney-Cd and liver-Cd data, the weighted mean BB-Cd was 50 mg. A minimum detectable BB-Cd of 21 mg was estimated from the median MDC values of kidney-Cd and liver-Cd. Correlations between the BB-Cd and B-Cd ($rs=0.45$, $P=0.044$) or U-Cd ($rs=0.78$, $P<0.001$) were noted.

Discussion

Previous studies have shown that x ray fluorescence can be used to measure kidney-Cd in occupationally exposed subjects, as well as in

Table 2   Prevalence of β_2-microglobulinuria (> 25 µg per mmole creatinine) in relation to the estimated liver-Cd and kidney-Cd

	Cases with β_2-microglobulinuria n(%)	Total number of cases
Liver-Cd (µg/g):		
< 5	1 (6)	15
5-10	1 (25)	4
> 10	4 (50)	8
Kidney-Cd (µg/g):		
< 50	1 (8)	13
50-100	2 (25)	8
100-150	2 (40)	5
> 150	0 (0)	3

the general population.[11][25] In the present study, we report for the first time the measurement of liver-Cd by x ray fluorescence.

The measurement of cadmium in the superficial liver tissue is favoured by a detection limit which is an order of magnitude lower than in measurement of the kidney-Cd. It is of interest to compare the presented kidney-Cd and liver-Cd with the respective detection limits for the two organs. Half of the workers in this study had liver-Cd above the MDC, whereas two thirds had kidney-Cd above the individual MDC. Furthermore, it is easier to find the liver and to keep the error in the measurement of position low. Also, the liver is less deeply situated than the kidney and the liver-Cd seems to be more uniform than the kidney-Cd. So, measurement of liver-Cd is preferable. For occupationally exposed people, liver-Cd can be high even when kidney-Cd is low. This may be due to induced kidney dysfunction. To estimate the cadmium body burden, liver-Cd may therefore be a better index than kidney-Cd. On the other hand, kidney-Cd is generally higher than liver-Cd, and from a toxicological point of view, the kidney is the critical organ. In summary, if the person's exposure history is unknown, measurements should be carried out in both kidney and liver.

Our results for kidney-Cd are in accordance with data from x ray fluorescence[9-11] and neutron activation analysis[26-36] in previous studies of occupationally exposed subjects. Unfortunately, the numerical results from studies with x ray fluorescence and neutron activation analysis cannot be directly compared. As the neutron activation analysis technique measures the total content of kidney-Cd, a conversion to a cadmium concentration in the cortex must be made. The conversion includes assumptions about the kidney weight and the relation between the mean concentration of kidney-Cd and the concentration in the cortex. The between subject variation in the average weight of a kidney can be considerable (SD 42 g, range 94-245 g).[37] There is also a variation of the relative volumes of medulla, cortex, and the whole kidney, whereas the conversion factor between the mean concentration of kidney-Cd and the mean cadmium concentration in the cortex seems to be similar (about 1.2-1.3) for most people.

The range of the liver-Cd is in agreement with or somewhat less than that found in neutron activation analysis studies.[27-35][38] The decrease in liver-Cd is supposed to be characterised by a faster half life (about five years),[32] compared with the kidney-Cd half life (about 10-30 years) as estimated from longitudinal studies of the decrease of B-Cd in retired workers.[39][40] Thus, the subjects' liver-Cd values in the present study may have been higher earlier but due to retirement and decreasing exposures over the years, they may have decreased.

The data in the present study describe a non-linear relation between kidney-Cd and liver-Cd, also seen in other in vivo studies,[27][28][30][34][35] which included people with normal kidney function as well as subjects with kidney damage. The kidney-Cd seems to increase linearly with liver-Cd up to a concentration at which the liver-Cd is about 20-30 µg/g, after which kidney-Cd decreases due to kidney dysfunction. Accordingly, liver-Cd has been proposed as a more reliable indicator of cadmium body burden in cases of kidney damage.[38]

The ratio between kidney-Cd and liver-Cd was broadly consistent with the ratios between 3 and 8, derived from other studies of occupationally exposed people.[27][28][30][33-35] (For these references we have calculated the ratios we have given from published values (arithmetic or geometric mean, or median) for the kidney cortex and liver.) For members of the general public, the ratio seems to be higher (11-39).[30][33-35][41-43] Assuming a faster elimination of liver-Cd, the ratio would increase if the occupational exposure stopped. Also, it must be stressed that the calculated ratios from some of the studies of exposed workers mentioned were obtained for subject groups which contained a fraction of subjects with kidney dysfunction. Thus, for those subjects the kidney-Cd may have decreased faster than the liver-Cd. This will also tend to lower the ratio.

The subject with kidney-Cd of 355 µg/g, but without signs of kidney dysfunction retired three years before this study but his B-Cd and U-Cd were still among the highest in the group. The combination of a very high kidney-Cd and a normal kidney function has been reported by others.[27][31][32] A hypothesis is that there is a proportion of people who are resistant to renal dysfunction induced by cadmium, and others are more sensitive.[44]

The B-Cd and U-Cd are influenced by the current and past exposure. Part of B-Cd reflects the body burden, but a substantial part is related to the exposure during the past few months.[39][45] Our results confirm previous findings[46] that current concentrations of B-Cd may be used to estimate the BB-Cd. The correlation coefficient is equal to the one presented by Roels *et al*[27] in a subgroup of workers with normal kidney function. The correlations between U-Cd, on one hand, and kidney-Cd or liver-Cd, on the other, imply that U-Cd reflects the BB-Cd after long term exposure, if no tubular damage has occurred. This is consistent with earlier published results.[24][27][45] Two earlier Swedish studies[10][11] showed no correlation between U-Cd and kidney-Cd. This might be caused by the fact that in those studies most workers (17 of 20) were currently exposed, whereas in the present study about half of the subjects were retired and the rest had had relatively low exposure during later years of work.

No correlations could be found between the estimated CumAir-Cd and the measured kidney-Cd and liver-Cd. This may partly be explained by the uncertainties in the estimated and measured variables. Thus, we have not yet been able to validate the total cadmium exposure as estimated by air cadmium concentrations and expressed as CumAir-Cd by means of concentrations of cadmium measured in vivo. Even if the individual CumAir-Cd values had been accurately measured, they are not

expected to be totally predictive of the cadmium intake, as this is influenced also by oral intake and respiratory function.

The BB-Cd values ranged up to 240 mg, and the mean was 50 mg. This is eight times higher than the value reported for occupationally unexposed Swedes.[24] However, for highly exposed workers the mean can be up to 200 mg.[27] [31] [33] [34] [36]

The figures used for calculation of the BB-Cd can be questioned. The data of Nordberg et al[24] stated that the fractions of the BB-Cd from the kidneys and the livers are about 50%-56% and 14%-18%, respectively. It was also reported that a greater proportion of the BB-Cd comes from the liver at higher exposures. On the other hand, a Japanese study of occupationally unexposed subjects ended up with corresponding figures of 36% and 26%.[47] Thus, a reasonable estimate for toxicological evaluations has been proposed, that one third of the BB-Cd is in the two kidneys.[24]

As already mentioned the variation in the kidney weight can be considerable. Moreover, the 80% range for the liver weight of middle aged men has been estimated to be 1500-2300 g.[23] Animal experiments on liver tissue suggested that there might be a somewhat higher accumulation of cadmium in the periphery of the liver lobes.[24] There is also an associated uncertainty as, generally, not all of the cadmium content of body organs is measured in necropsy studies. Thus, the variation in these variables and the uncertainty in the x ray fluorescence measurement are responsible for the differences found in the body burden estimated from the kidney-Cd and liver-Cd, separately.

The B-Cd, U-Cd, and kidney-Cd were not different between subjects with and without kidney dysfunction. On the other hand, liver-Cd was higher for people with β_2-microglobulinuria. This indicates that liver-Cd can remain at a high value in cases with kidney damage. The same result was found when another commonly used cut off point for U-β_2-m (34 µg/mmol creatinine) was used.

Table 2 also indicates a relation between the liver-Cd and the prevalence of β_2-microglobulin in the urine. Roels et al[27] and Ellis et al[31] showed that whenever a person's liver-Cd exceeded 30-40 µg/g and CumAir-Cd 400-500 µg/m³.y, there was evidence of kidney dysfunction. Our material contains only one subject with such a high liver-Cd value, and he did have renal damage.

In conclusion, the x ray fluorescence turned out to be practically useful for measurements of liver-Cd. The U-Cd could be used to predict both liver-Cd and kidney-Cd. The relation between the kidney-Cd and the liver-Cd was in keeping with the non-linear shape found by others. However, in vivo measurements of kidney-Cd and liver-Cd did not correlate with the cadmium exposure estimates obtained as CumAir-Cd.

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