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Markers of early renal changes induced by industrial pollutants. II Application to workers exposed to lead

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Abstract

The present study has been carried out in the framework of a collaborative research project on the development of new markers of nephrotoxicity. A battery of more than 20 potential indicators of renal changes has been applied to 50 workers exposed to lead (Pb) and 50 control subjects. After application of selection criteria 41 exposed and 41 control workers were eventually retained for the final statistical analysis. The average blood Pb concentration of exposed workers was 480 μg/l and their mean duration of exposure was 14 years. The battery of tests included parameters capable of detecting functional deficits (for example, urinary proteins of low or high molecular weight), biochemical alterations (for example, urinary eicosanoids, glycosaminoglycans, sialic acid) or cell damage (for example, urinary tubular antigens or enzymes) at different sites of the nephron or the kidney. The most outstanding effect found in workers exposed to Pb was an interference with the renal synthesis of eicosanoids, resulting in lower urinary excretion of 6-keto-PGF$_{1\alpha}$ and an enhanced excretion of thromboxane (TXB$_2$). The health significance of these biochemical alterations, detectable at low exposure to Pb is unknown. As they were not associated with any sign of renal dysfunction, they may represent reversible biochemical effects or only contribute to the degradation of the renal function from the onset of clinical Pb nephropathy. The urinary excretion of some tubular antigens was also positively associated with duration of exposure to Pb. Another effect of Pb that might deserve further study is a significant increase in urinary sialic acid concentration.

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Excessive exposure to lead (Pb) may cause acute or chronic nephrotoxic effects.[1–10] Acute Pb nephropathy is characterised functionally by a generalised deficit of tubular transport mechanisms (Fanconi syndrome) and morphologically by the appearance of degenerative changes in the tubular epithelium and nuclear inclusion bodies containing Pb protein complexes.[10–12] These effects, which are usually reversible with chelation therapy, have been reported mainly in children.[9–12] Chronic Pb nephropathy is an irreversible renal disease that develops over months or years of excessive exposure and which may be associated with gout and hypertension.[9–11 13] This has been reported in adults who had ingested leaded paint during childhood (Queensland, Australia), who had consumed illicitly distilled alcohol ("moonshine whisky"), or who had a long history of occupational exposure.[9 10 12 14] In the chronically exposed adult, Pb nephropathy occurs as a progressive tubulointerstitial nephritis that is difficult to diagnose at the early stage. Indeed incipient Pb nephropathy is not associated with urine abnormalities easily detected by dipsticks. Tests evaluating the glomerular filtration rate (creatinine clearance, blood urea nitrogen, or serum creatinine) are the only ones which presently can be used to detect renal effects caused by occupational exposure to Pb.[9 15 16] But when these tests are abnormal, then nephropathy has already reached an irreversible phase that may lead to renal insufficiency.[16] More sensitive markers would be useful

to ensure that occupational exposure levels to Pb currently prevailing in the industry do not entail a risk for renal function

One of the metals examined in the framework of a collaborative research project on the development and validation of new markers of nephrotoxicity was Pb. In this project we investigated more than 20 potential markers of renal effects that can be arbitrarily classified into three broad categories—namely, functional markers (for example, urinary proteins), cytotoxicity markers (for example, tubular antigens), and biochemical markers (for example, eicosanoids). These markers were applied to a cohort of 50 workers moderately exposed to Pb to assess whether they may be useful for the early detection of renal effects caused by this metal.

Subjects and methods

STUDY POPULATION

The control and exposed workers recruited for this study, 50 in each group, were employed in a Pb smelter in Belgium. To be included in the exposed group, workers should have at the time of examination a blood Pb concentration (Pb-B) above 350 μg/l with a duration of exposure of at least one year. The control and exposed groups were then subjected to a careful selection (see reference 17 for a detailed description of the criteria) to exclude subjects whose renal function might be altered by causes other than Pb. Forty one workers were finally retained in each cohort.

METHODS

Blood and urine samples were collected as described in the paper on the mercury cohort.[17] An identical battery of tests was also applied comprising: in blood, lead and zinc protoporphyrin (ZPP) concentrations, alcian blue (AB) binding to red blood cell (RBC) surfaces, sialic acid content of RBC membranes; in serum or plasma, creatinine (crt-S), β_2-microglobulin (β_2-m), anti-GBM antibody (anti-GBM) and sialic acid concentrations; and in urine, cadmium (Cd-U), mercury (Hg-U), sodium, creatinine (crt-U), albumin, transferrin, immunoglobulin (IgG), β_2-m, retinol binding protein (RBP), protein 1, Tamm-Horsfall glycoprotein (THG), fibronectin, 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), thromboxane B_2 (TXB_2), sialic acid, glycosaminoglycan (GAG), the brush border antigens (BBA, BB50 and HF5) concentrations, pH, and activities of kallikrein, intestinal alkaline phosphatase (IAP), tissue non-specific alkaline phosphatase (TNAP), and N-acetyl-β-D-glucosaminidase (NAG). The urinary concentration of δ-aminolaevulinic acid (ALAU) was determined by an automated technique.[18] Statistical analysis was performed as described earlier.[17]

Results

Table 1 shows the characteristics of the controls and workers exposed to Pb. The duration of exposure ranged from two to 33 years (mean 14 years). Compared with the referents, the workers exposed to Pb were on average older and they excreted more creatinine and cadmium in urine but less mercury. The smoking and drinking habits of the two groups were similar. In the control workers ZPP concentra-

Table 1 Characteristics of control and workers exposed to Pb

	Control workers (n = 41)		*Exposed workers (n = 41)*		
	Mean or No	*SD or (range)*	*Mean or No*	*SD or (range)*	*p Value**
Age (y)	35·0	8·1	39·0	9·2	<0·05
Body mass index	24·4	3·5	25·4	3·2	NS
Smokers	15		21		NS
Duration (y)	14·1	9·2	16·7	6·8	NS
Cigarettes/day	12·9	5·6	17·2	10·4	NS
Alcohol drinkers	26		25		NS
Glasses/week	14·7	9·2	17·9	12·4	NS
Exposure (y)	—		14·0	7·0	—
Pb-B (μg/l)	167	(63–343)	480	(363–646)	<0·0001
ZPP in blood† (μg/g Hb)	1·12	(0·60–3·1)	3·41	(1·30–13·6)	<0·001
ALA in urine † (mg/l)	5·1	(1·4–11·6)	7·6	(1·2–40·6)	<0·01
ALA in urine† (mg/g creatinine)	4·8	(3·0–8·1)	5·8	(3·2–17·9)	<0·01
Cd in urine† (μg/l)	0·43	(0·08–1·86)	1·17	(0·37–1·86)	<0·001
Cd in urine† (μg/g creatinine)	0·40	(0·30–1·90)	0·88	(0·30–1·90)	<0·001
Hg in urine† (μg/l)	2·5	(1·4–7·1)	2·3	(1·3–6·8)	NS
Hg in urine† (μg/g creatinine)	2·3	(1·0–4·7)	1·7	(0·8–4·9)	<0·01
Creatinine in urine (g/l)	1·18	(0·40–2·41)	1·56	(0·31–3·51)	<0·05

*Student's t test or χ^2 test.
†Geometric means.

Table 2 Significant associations found by multiple regression analysis

*Dependent variables**	*Independent variables**	*Partial regression coefficient*	*Partial r^2*	*p Value*
Urine:				
Albumin	Crt-U	0·813	0·381	0·0001
Transferrin	Crt-U	0·864	0·304	0·0001
IgG	Crt-U	0·701	0·306	0·0001
β_2-m	Crt-U	0·456	0·123	0·0007
	BMI	−0·035	0·101	0·0037
RBP	Crt-U	0·954	0·634	0·0001
Protein 1	Crt-U	0·834	0·302	0·0001
THG	Crt-U	1·238	0·820	0·0001
NAG	Crt-U	0·576	0·410	0·0001
BB50†	Crt-U	0·652	0·246	0·0001
	BMI	−0·017	0·036	0·0492
BBA†	Crt-U	0·481	0·165	0·0002
HF5†	Crt-U	0·543	0·178	0·0001
IAP	Crt-U	1·084	0·392	0·0001
TNAP	Crt-U	1·863	0·266	0·0001
	BMI	−0·054	0·050	0·0186
Fibronectin	Crt-U	0·320	0·309	0·0001
6-keto-$PGF_{1\alpha}$	Crt-U	0·603	0·524	0·0001
	Pb-B	−0·179	0·056	0·0018
PGE_2	Crt-U	0·625	0·241	0·0001
	BMI	−0·018	0·048	0·0258
$PGF_{2\alpha}$	Crt-U	1·208	0·563	0·0001
TXB_2	Crt-U	0·486	0·355	0·0001
	Pb-B	0·360	0·170	0·0001
Kallikrein	Crt-U	0·910	0·499	0·0001
GAG	Crt-U	0·700	0·787	0·0001
Sialic acid	Crt-U	0·921	0·526	0·0001
	ZPP	0·205	0·037	0·0118
pH urine	BMI	−0·096	0·229	0·0001
	Crt-U	−1·073	0·105	0·0007

*Pb-B, ZPP, and urinary variables were log transformed. All urinary parameters were expressed per litre.
†Correlated with duration of exposure in the exposed group.
For abbreviations see subjects and methods section.

tions did not exceed the upper normal value of 2·5 μg/g Hb, except in one worker (3·1 μg/g Hb). The workers exposed to Pb showed significantly increased ZPP and ALAU concentrations compared with the control group. The different indicators of exposure to Pb were positively related to each other. Pearson's correlation coefficients ($p < 0·001$) and regression lines (within parentheses) were calculated on the total population ($n = 82$): $r = 0·80$ between ZPP and Pb-B (log ZPP = −2·12 + 9·98 log Pb-B); $r = 0·52$ between ALAU (factored for creatinine) and ZPP (log ALAU = 0·65 + 0·240 log ZPP); and $r = 0·38$ between ALAU and Pb-B (log ALAU = 0·19 + 0·218 log Pb-B). No relation existed between Pb-B or ZPP and the duration of exposure.

No statistically significant association was found between the renal variables and age in the control group. Multivariate correlation analysis on the total population ($n = 82$) showed that the excretions of 6-keto-$PGF_{1\alpha}$ and TXB_2 in urine were significantly correlated with Pb-B in a negative and positive fashion respectively, whereas the urinary excretion of sialic acid was positively associated with ZPP (table 2). To assess the influence of the duration of exposure on the renal parameters a multivariate correlation analysis was also performed on the Pb workers. Only the tubular antigens BB50, BBA, and HF5 were found to be significantly related to the duration of exposure.

After adjustment of the renal parameters for the interfering factors recorded in table 2 (mainly crt-U and sometimes also body mass index (BMI)) the only significant findings in the workers exposed to Pb were an increase in the mean urinary excretion of TXB_2, NAG, and sialic acid, and a decrease in 6-keto-$PGF_{1\alpha}$ (table 3). The comparison of prevalences of abnormal values (table 4) showed a similar pattern of changes with, in addition, a higher prevalence of reduced PGE_2 values in urine in the workers exposed to Pb.

Before standardisation for confounding factors, urinary pH was lower in workers exposed to Pb than in controls (6·05 *v* 6·85 in controls, $p < 0·01$). This effect, however, was not significantly related to any marker of Pb exposure (table 2). It was probably responsible for some degradation of β_2-m as suggested by a significant correlation between both

Table 3 Urinary and bloodborne markers of nephrotoxicity in control and workers exposed to Pb

Marker	*Control workers (n = 41)§ Mean (SD or range)*	*Exposed workers (n = 41)‖ Mean (SD or range)*	*p Value**
Urine:†			
Albumin (mg/l)	5·8 (2·6–53·1)	6·5 (3·0–28·5)	NS
Transferrin (μg/l)	215 (83–2280)	254 (46–1234)	NS
IgG (μg/l)	1269 (320–3682)	1189 (338–4175)	NS
β_2-m (μg/l)	72 (15–477)	57 (13–170)	NS
RBP (μg/l)	64 (35–238)	68 (33–174)	NS
Protein 1 (μg/l)	86 (21–636)	95 (16–332)	NS
THG (mg/l)	16·2 (8·8–41·0)	16·6 (9·1–31·0)	NS
NAG (U/l)	1·21 (0·49–2·93)	1·56 (0·82–5·21)	<0·01
BB50 (U/l)	9·3 (2·8–34·7)	11·0 (2·0–38·8)	NS
BBA (U/l)	7·7 (2·7–28·1)	9·0 (2·2–52·5)	NS
HF5 (U/l)	6·9 (1·2–30·2)	8·2 (3·0–44·9)	NS
IAP (U/l)	0·53 (0·14–2·04)	0·54 (0·08–4·49)	NS
TNAP (U/l)	0·081 (0·005–0·704)	0·091 (0·003–1·40)	NS
Fibronectin (μg/l)	14·6 (7·5–28·7)	13·8 (8·6–35·6)	NS
6-keto-$PGF_{1\alpha}$ (ng/l)	180 (120–270)	140 (47–291)	<0·001
PGE_2 (ng/l)	135 (73–533)	118 (41–412)	NS
$PGF_{2\alpha}$ (ng/l)	192 (65–501)	204 (45–891)	NS
TXB_2 (ng/l)	43 (19–84)	69 (33–133)	<0·001
Kallikrein (U/l)	0·72 (0·17–2·18)	0·75 (0·29–2·08)	NS
GAG (mg/l)	38·5 (27·3–52·1)	38·3 (17·9–54·0)	NS
Sialic acid (mg/l)	215 (106–1073)	308 (128–613)	<0·01
Blood:‡			
Creatinine/serum (mg/l)	10·3 (1·0)	10·2 (1·0)	NS
β_2-m/serum (mg/l)	1·37 (0·27)	1·42 (0·34)	NS
Sialic acid/plasma (mg/l)	708 (157)	723 (238)	NS
Sialic acid/RBC (μg/mg protein)	29·3 (5·5)	28·9 (4·4)	NS
AB binding/RBC (ng/10^6 RBC)	184 (25)	185 (21)	NS
Anti-GBM/serum (U/l)	26·6 (6·1)	24·6 (4·9)	NS

*Student's *t* test.
†Geometric means; ‡Arithmetic means.
§For PGE_2 n = 39.
‖For PGE_2 and kallikrein n = 40 and 38 respectively.
For abbreviations see subjects and methods section.
All the markers of nephrotoxicity were standardised for the determinants unrelated to Pb exposure (see table 2). Standardisation was based on the mean of the total population.

variables ($r = 0{\cdot}68$, $p = 0{\cdot}0001$; log β_2-m $= -0{\cdot}77 + 3{\cdot}09$ log pH). In the multivariate analysis, 48% of the variance in β_2-m excretion was explained by urinary pH. This again confirms that making urine alkaline after collection is not a satisfactory procedure for avoiding the degradation of β_2-m.

The exposed workers were divided into two subgroups according to Pb-B (Pb-B $\leqslant$ 500 and Pb-B > 500 μg/l) and ZPP (ZPP $\leqslant$ 5 and ZPP > 5 μg/g Hb) and the prevalences of abnormal values were compared (figs 1 and 2). A few parameters showed a tendency for a dose-response relation such as the increased urinary excretion of sialic acid with Pb-B and ZPP, and the decreased excretion of 6-keto-$PGF_{1\alpha}$ and PGE_2 with ZPP.

Discussion

Renal effects of Pb, consisting mainly in a decline of the glomerular filtration rate without proteinuria, have been reported in workers with longstanding exposure to Pb and with Pb-B of 600 μg/l or more.[1–8] So far, studies conducted on populations of workers with lower levels of exposure to Pb have disclosed no renal effect or only infraclinical changes of marginal significance.[14 19–22] The cohort of workers examined in the present study had an average Pb-B of 480 μg/l and only three workers had a value above 600 μg/l (highest value 646 μg/l). After standardisation for factors unrelated to Pb exposure, three renal effects—namely, a reduced urinary excretion of 6-keto-$PGF_{1\alpha}$ and an increased excretion of TXB_2 and sialic acid (table 2) were found to be statistically associated with Pb-B or ZPP. No statistically significant changes in the urinary excretion of tubular antigens or specific low or high molecular weight proteins were found. The urinary excretion of the tubular antigens BB50, BBA, and HF5, however, was related to the duration

Table 4 Prevalences of abnormal values of urinary and bloodborne markers of nephrotoxicity in controls and workers exposed to Pb

Marker	Cut off value†	Control workers (n = 41)‡ No	(%)	Exposed workers (n = 41)§ No	(%)	p Value*
Urine:†						
Albumin	>12·2	2	(4·9)	8	(19·5)	NS
Transferrin	>567	2	(4·9)	8	(19·5)	NS
IgG	>3141	2	(4·9)	1	(2·4)	NS
β_2-m	>164	2	(4·9)	1	(2·4)	NS
RBP	>101	2	(4·9)	7	(17·1)	NS
Protein 1	>271	2	(4·9)	3	(7·3)	NS
THG	>28·1	2	(4·9)	1	(2·4)	NS
NAG	>2·21	2	(4·9)	4	(9·8)	NS
BB50	>18·6	2	(4·9)	7	(17·1)	NS
BBA	>17·6	2	(4·9)	5	(12·2)	NS
HF5	>17·8	2	(4·9)	4	(9·8)	NS
IAP	>1·56	2	(4·9)	4	(9·8)	NS
TNAP	>0·48	2	(4·9)	6	(14·6)	NS
Fibronectin	>19·8	2	(4·9)	2	(4·9)	NS
6-keto-$PGF_{1\alpha}$	<135	2	(4·9)	16	(39·0)	<0·001
PGE_2	<77	2	(5·1)	10	(25·0)	<0·05
$PGF_{2\alpha}$	<79	2	(4·9)	5	(12·2)	NS
TXB_2	>77	2	(4·9)	16	(39·0)	<0·001
Kallikrein	<0·36	2	(4·9)	4	(10·5)	NS
GAG	>51	2	(4·9)	4	(9·8)	NS
Sialic acid	>380	2	(4·9)	21	(51·2)	<0·0001
Blood:						
Creatinine/serum	>11·7	2	(4·9)	2	(4·9)	NS
β_2-m/serum	>1·88	2	(4·9)	4	(9·8)	NS
Sialic acid/plasma	>958	2	(4·9)	6	(14·6)	NS
Sialic acid/RBC	<21·9	2	(4·9)	3	(7·3)	NS
AB binding/RBC	<150	2	(4·9)	1	(2·4)	NS
Anti-GBM/serum	>36·7	3	(7·3)	0	—	NS

*Fisher's exact test.
†For units see table 3 and for abbreviations see subjects and methods section.
‡For PGE_2 n = 39.
§For PGE_2 and kallikrein n = 40 and 38 respectively.
All the markers of nephrotoxicity were standardised for the determinants unrelated to Pb exposure (see table 2). Standardisation was based on the mean of the total population.

of exposure. Hence, a slight tubulotoxic effect of Pb cannot be formally excluded.[23]

An intriguing finding was the slightly increased urinary NAG activity in workers exposed to Pb (table 3). This seems to agree with three cross sectional studies in which a significant increase in activity of NAG was found in workers with mean Pb-B values below 600 μg/l.[24-26] Besides the fact that the increased urinary activity of NAG was not always dose related[24] or uncorrected for diuresis, [25] these studies did not take into account the simultaneous exposure to cadmium that occurs frequently in Pb smelters. Actually, in the present study we implicitly assumed that cadmium would not cause renal effects when Cd-U did not exceed 2 μg/g creatinine as suggested by studies on cadmium workers[27] and in the general population.[28] The prevalence of abnormal NAG values was not, however, correlated with Pb-B (fig 1) or ZPP (fig 2), nor with duration of exposure to Pb. Furthermore, a positive association was found with Cd-U (log NAG = 0·18 + 0·20 log Cd-U (μg/g creatinine), r = 0·39, p < 0·0005). In another study on workers exclusively exposed to Pb (without concomitant increased Cd-U) no significant change in activity of NAG was found (unpublished results). Taken together, the results suggest that the increase in activity of NAG found in the present and other studies among workers exposed to Pb[24-26] might be caused by a combined effect of Pb and cadmium. It is also possible that the association between Cd-U and NAG activity was simply the expression of a simultaneous increase in cadmium and NAG excretion as the result of some tubular changes induced by Pb.[29]

The absence of change in the urinary excretion of low molecular weight proteins is in agreement with previous studies that failed to show an increase in β_2-m excretion even in workers highly exposed to lead.[15 19 21 30 31] The only exceptions are the studies of

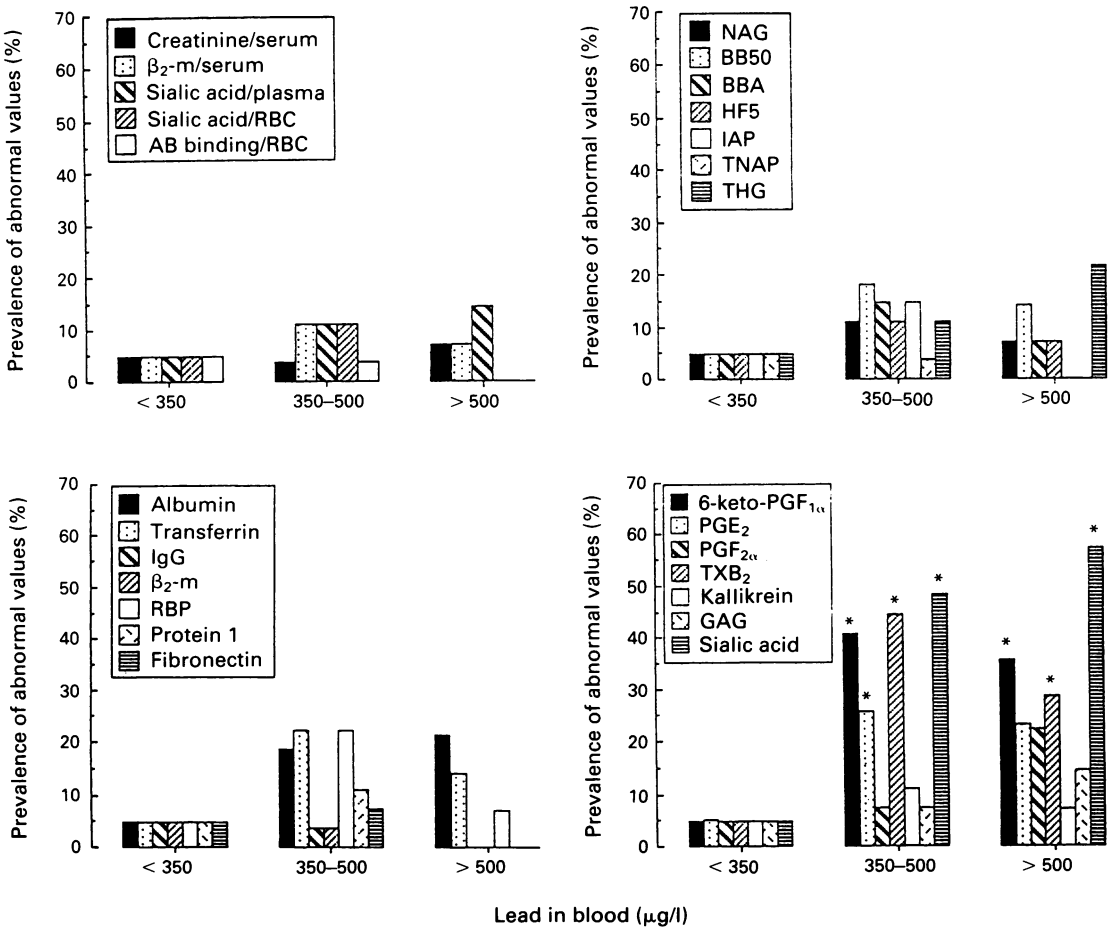

*Figure 1 Prevalences of abnormal values of markers of nephrotoxicity as a function of Pb-B. Prevalences were established on the basis of the cut off values given in table 4. The numbers of subjects in each group were 41 (controls: Pb-B < 350 μg/l), 27 (Pb-B ≤ 500 μg/l), and 14 (Pb-B > 500 μg/l). The mean duration of exposure of the two Pb subgroups were 15·6 and 10·9 years respectively. *Significantly different from the group with Pb-B < 350 μg/l.*

Verschoor *et al*[26] and of Huang *et al.*[32] The last authors reported an increase in β_2-m excretion in workers exposed to Pb but this was not substantiated by a comparison with a matched control group and no attempt was made to correlate this effect with indicators of exposure to Pb. Verschoor *et al*[26] found a slight increase in urinary RBP, but this was not correlated with the Pb-B level and therefore might well be caused by another factor. In support of this Mason and co-workers[33] found no increase in excretion of RBP in workers with chronic high exposure to Pb.

The most interesting effects of exposure to Pb unravelled by the present study are the changes in the urinary excretion of eicosanoids, which likely reflect a disturbance in their synthesis. These changes might be involved in the progressive loss of renal function or in the development of hypertension seen in some subjects with a long history of excessive exposure to Pb. Abnormalities in renal metabolism of prostaglandin and thromboxane may contribute to the pathophysiology of renal failure and hypertension.[34] In essential hypertension, for instance, the urinary excretion of PGE_2 and 6-keto-$PGF_{1\alpha}$ (two vasodilatators) has been reported to be decreased whereas that of TXB_2 (a vasoconstrictor derived from arachidonic acid) was increased.[34] As well as a direct vasoactive action that results in an increased renal vascular resistance, the depletion of prostaglandins seems to enhance the retention of sodium and the pressor response to angiotensin II and vasopressin.[34–37] Workers exposed to Pb seem to have

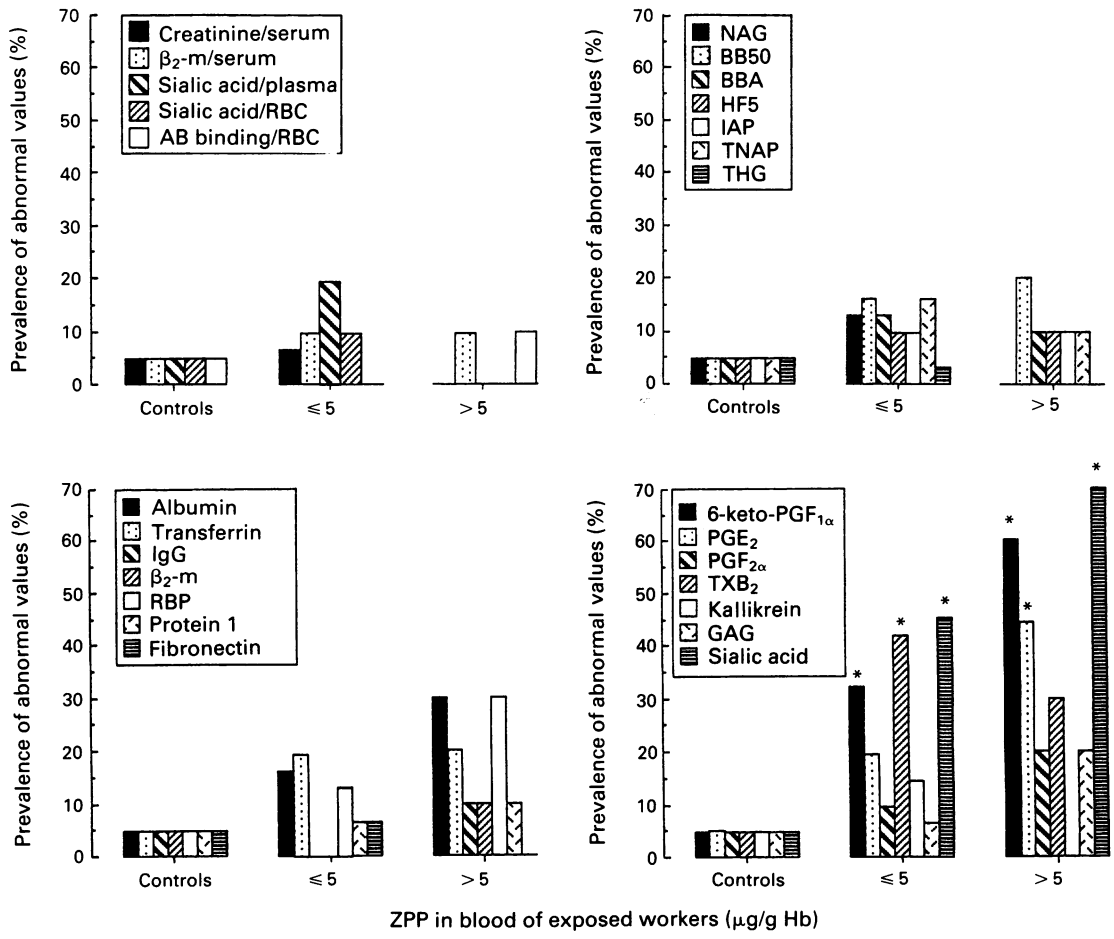

*Figure 2 Prevalences of abnormal values of markers of nephrotoxicity as a function of ZPP concentrations. Prevalences were established on the basis of the cut off values given in table 4. The numbers of subjects in each group were 41 (controls), 31 (ZPP ≤ 5 μg/g Hb), and 10 (ZPP > 5 μg/g Hb). The mean duration of exposure of the two lead subgroups were 13·7 and 14·9 years respectively. *Significantly different from the control group.*

a diminished synthesis of PGE_2 and 6-keto-$PGF_{1\alpha}$ in the kidney together with an enhanced production of TXB_2. Thus Pb might produce changes in the renal metabolism of eicosanoids that mimic those occurring in essential hypertension.

The most remarkable is that effects on excretion of eicosanoids in urine are already detectable at exposures to Pb that are rather low. This finding might be relevant for the current controversy on the effects of Pb on blood pressure in the general population.[37 38] The early effects on urinary excretion of 6-keto-$PGF_{1\alpha}$ and TXB_2 suggest that the initial insult in Pb nephropathy might also involve the vasculature and glomeruli, and is not exclusively localised in the tubulointerstitial compartment. The changes in the renal synthesis of eicosanoids raise the question of their relevance to health. Are these changes the reflection of an ongoing degenerative process that may lead to a loss of renal function or do they simply represent biochemical effects of Pb without any clinical significance? The failure in the present study to show any significant renal impairment in the workers exposed to Pb, despite the application of a large battery of markers, is more in favour of the second hypothesis. It should be stressed, however, that changes in prostaglandin production, which normally exert little influence on renal haemodynamics, may have deleterious consequences in conditions of decreased renal perfusion. Therefore it is possible that the changes reported may precipitate the decline in renal function only at exposure levels to Pb giving rise to additional nephrotoxic effects or

when the kidney is submitted to other toxic insults.

Another mechanism that has been postulated in the development of Pb hypertension is a reduced synthesis of kallikrein.[39] The urinary activity of this vasodilation mediating enzyme has been found to be decreased in workers with heavy exposure to Pb.[39–41] In the present study, however, as in a previous one,[42] no effect of exposure to Pb on urinary kallikrein activity could be found, even when the exposed group was subdivided into young and old workers (results not shown). Thus if kallikrein is involved in the haemodynamic response to exposure to Pb, it is probably from an exposure level higher than that interfering with production of eicosanoids.

The increased urinary excretion of sialic acid also appears as a rather early effect of exposure to Pb. An increase in urinary sialic acid has also been seen in cadmium workers with proteinuria.[27 43] In workers exposed to Pb, the enhanced excretion of sialic acid cannot be explained by an increased urinary output of plasma proteins or enzymes as no abnormality was found in these parameters. The hypothesis of a biochemical disturbance, unrelated to renal function, appears more probable. As most urinary sialic acid is bound to glycoproteins or glycoderivatives, it would be interesting to identify the specific constituents responsible for the increase of sialic acid in urine.

In conclusion, the early renal effects of occupational exposure to Pb found in the present study consist of decreased urinary excretion of 6-keto-$PGF_{1\alpha}$ associated with enhanced excretion of thromboxane. The relevance to health of these biochemical alterations, detectable at very low exposure to Pb, remains to be established. In view of the lack of any sign of renal dysfunction, however, it is possible that these changes in eicosanoid metabolism correspond to reversible biochemical effects and may only contribute to the degradation of renal function from the onset of the clinical Pb nephropathy. Another effect found in workers exposed to Pb, which might deserve further investigation, is the significant increase in urinary sialic acid.

Appendix

CONVERSION OF UNITS

Lead	1 μg = 4·83 nmol
Cadmium	1 μg = 8·90 nmol
Mercury	1 μg = 4·99 nmol
Creatinine	1 g = 8·84 mmol

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