Abstract: Scintigraphic assessment of renal function in steel plant workers occupationally exposed to lead: Teresa WROŃSKA-NOFER, et al. Department of Toxicology and Carcinogenesis, Nofer Institute of Occupational Medicine, Poland—Objectives: Occupational exposure to lead may produce kidney damage, but existing data on the dose range associated with nephrotoxicity are inconclusive. We here assessed renal function under conditions of low to moderate lead exposure using renal scintigraphy. Methods: Fifty-three male foundrymen (exposed group) and forty male office workers (control group) from a steel plant were included in the study. Glomerular and tubular renal function were assessed by means of $^{99m}$Tc-DTPA and $^{99m}$Tc-EC clearance, respectively. Urinary markers of glomerular dysfunction (albumin) and tubular damage ($\alpha_1$-microglobulin ($\alpha_1$M), $\beta_2$-microglobulin ($\beta_2$M), retinol-binding protein (RBP), $\alpha_2$-acid-glycoprotein (NAG) activity) were determined using latex beads tests or colorimetry. The lead concentration in blood was assessed using atomic absorption spectrometry. The results were presented with increased $^{99m}$Tc-DTPA clearance (158.3 (148.4−168.8) ml/min; p<0.01) and urinary albumin excretion (7.61 (6.28−9.22) vs. 4.78 (148.4−168.8) vs. 135.9 (127.9−144.4) m$\mu$g/g creatinine; p<0.01) and between urinary albumin excretion and blood lead concentrations (r=0.45; p<0.01) and between urinary albumin excretion and blood lead concentrations (r=0.71; p<0.001) were noted. Conclusions: Use of renal scintigraphy in present study revealed measurable alterations of renal function under the conditions of low-level lead exposure and suggest that increased glomerular filtration may be an early indicator of kidney damage in subjects occupationally exposed to lead. (J Occup Health 2015; 57: 91–99)

Key words: Lead, Occupational exposure, Renal scintigraphy

Lead absorbed in the body is mainly excreted through kidneys, and longstanding exposure to excessive lead concentrations may cause chronic nephrotoxic effects such as interstitial nephritis, tubular damage, and at later stages glomerular damage leading to the chronic renal failure$^{1,2}$. Observational studies have repeatedly reported an association between lead exposure and an increased risk of renal disease, but the intensity of exposure, which ultimately produces renal damage, is still a matter of debate$^{3,4}$. Up to the present, severe adverse effects of lead on the kidney have been reported chiefly in subjects occupationally exposed in a working environment, which is the major source of heavy lead exposure$^{5,6}$. Bases on these results, the WHO Task Group on Environmental Health Criteria for Inorganic Lead concluded that renal dysfunction occurs in lead-exposed workers mainly at blood levels exceeding 600 $\mu$g/l$^{7}$. While most studies have failed to detect major adverse effects on kidney integrity in workers moderately exposed to lead, more subtle alterations manifesting as increased urinary excretion of sensitive tubular damage indicators such as $\alpha_1$-microglobulin ($\alpha_1$M), $\beta_2$-microglobulin ($\beta_2$M) or N-acetyl-$\beta$-glucosaminidase (NAG) have repeatedly
been detected in subjects, in whom the blood lead concentrations did not regularly exceed 600 µg/l\(^2\). In addition, moderate exposure to lead was found to produce increased plasma levels of uric acid arising as a consequence of defective tubular secretion and/or excessive tubular reabsorption\(^5,8-17\).

Previous investigations in subjects occupationally exposed to lead have usually employed traditional clinical parameters for the assessment of renal function such as blood urea nitrogen (BUN), serum creatinine, creatinine clearance, or urinary excretion of low-weight proteins, which are inaccurate and do not allow the functional impairment related to tubular damage to be clearly distinguished from that related to glomerular damage. In the present study, we applied dynamic scintigraphy with technetium-99m diethylenetriamine pentaacetic acid (\(^{99m}\text{Tc-DTPA}\)) and technetium-99m ethylenedycysteine (\(^{99m}\text{Tc-EC}\)) along with early markers of renal damage for the first time in a group of foundrymen and crane operators chronically exposed to lead in the ambient air at low to moderate levels. Renal scintigraphy is characterized by enhanced precision and enables complex assessment of various kidney functions including glomerular filtration, tubular excretion and urine outflow.

Our results suggest that even low to moderate occupational exposure to lead may give rise to measurable alterations in kidney functions, which encompass glomerular hyperfiltration and increased albumin excretion.

**Material and Methods**

**Study subjects**

This study recruited 93 male employees of steel plant located in the south-eastern part of Poland that produces steel in an electric arc furnace (EAF) process using metal scrap as the sole charge. All included subjects were between 35 and 56 years of age and had employment histories of 11 to 36 years. The exposed group was made up of 53 foundrymen and crane operators participating in continuous steel casting and having contact with various impurities (dust and toxic chemicals including lead). As a rule, they used to stay in the polluted melt-shop area not less than 8 hours and worked for the entire period of their occupational activities in an environment polluted with heavy metals. While operating furnaces, foundrymen used half-masks equipped with a dust-absorbing filter. Monitoring conducted by the environmental health and safety (EHS) department of the steel plant revealed this group to be the most exposed among the staff. The control group consisted of 40 workers of the same steel plant allocated to administration, who have never been occupationally exposed to dust and/or heavy metals in the courses of their professional careers. All examined subjects received information on the purpose of the study and signed a participation consent form. The protocol was approved by the local ethics committee. Each subject underwent a general medical examination, and information concerning smoking and medication within the past 12 months was collected. Subjects with known hematological or kidney diseases or apparent symptoms of health deterioration (n=2) were excluded. Except for minor illnesses, subjects in both examined groups were in a good health and were examined once during the course of the study.

**Blood and urine sample collection**

Blood was collected in an outpatient station located outside the melt-shop area simultaneously in both groups during the working shift one day before the first renal scintigraphy was performed. Blood samples for lead analysis were obtained using heavy metal-free disposable syringes (Venosafe\(^\text{®}\) Li-Heparine, Terumo-Europe, Leuven, Belgium) certified for metal determination and stored until analysis at −20°C in lead-free bottles for the maximum period of 6 months. Serum was separated by centrifugation immediately after blood collection and stored as described above. Overnight urine samples were collected in the morning before a shift and temporarily stored at 4°C for no longer than 3 hours. To avoid contamination, polyethylene tubes were soaked in nitric acid (25%, v/v) for several hours and rinsed with ultrapure water prior to urine collection. Spot urine samples for cadmium determination (5.0 ml) were acidified with ultrapure nitric acid (0.05 ml, 50% v/v, Merck, Darmstadt, Germany). For the NAG and creatinine determination, samples were stored without any preservation. For determinations of β,M, α,M and retinol-binding protein (RBP), 0.5 ml of phosphate buffer (0.4 mol/l, pH 7.4) containing 1% sodium azide was added to 4.5 ml urine. Preliminary experiments revealed that such handling is sufficient to avoid degradation of β,M, which was reported to be unstable in a low pH environment\(^2\). Thereafter, samples were divided into aliquots and kept frozen at −20°C until analysis. According to previous studies\(^2\) and our own observations, urine storage at −20°C leads to marginal protein degradation, which is comparable to that seen at −70°C.

**Determination of occupational exposure indices**

For lead determination, blood samples (4.0 ml) were deproteinized with 1.6 ml nitric acid (5.0%, v/v). Samples were left for at least 1 hour at room temperature and centrifuged (11,500 rpm, 15 minutes, 4°C), and the supernatant was then transferred to autosampler tubes. Urine samples were diluted 1:1 (v/v) with a matrix modifier containing diammonium hydrogen
phosphate (0.5%, w/v) and magnesium nitrate (0.03%, w/v), and transferred to autosampler tubes. All vessels used during the analysis were washed with nitric acid (20.0%, v/v) and deionized water. The concentrations of lead in blood and cadmium in urine were determined using a graphite-furnace atomic-absorption spectrometer equipped with a transverse heated graphite atomizer and longitudinal Zeeman-effect background correction (Perkin-Elmer 4100ZL, Perkin Elmer, Palo Alto, CA, USA) as described previously\textsuperscript{24,25}. Signals for lead and cadmium were monitored at 283.3 and 228.8 nm, respectively, using a slit width of 0.7 nm. The electrodeless discharge lamp was operated at 10 mA and 4 mA, respectively. The injection temperature was 100°C, the argon flow was 0.25 l/min, and the read time was 3 seconds for both parameters. The graphite furnace temperature program is shown in Table 1. The precisions of lead and cadmium determination were estimated to be 5.0 and 6.1%, respectively. The limit of detection (LoD) and limit of quantitation (LoQ) were, respectively, 1.0 µg/l and 2.0 µg/l for lead and 0.10 µg/l and 0.18 µg/l for cadmium. External quality control was carried out under the UK National External Quality Assessment Scheme (UK NEQAS). The laboratory was accredited according to PN/EN ISO/IEC 17025 (Assessment Scheme (UK NEQAS). The laboratory was accredited according to PN/EN ISO/IEC 17025 to perform measurements of lead in blood and cadmium in urine for occupational medicine purposes.

**Early biomarkers of renal damage**

The concentrations of β\textsubscript{2}M, α\textsubscript{1}M, RBP and albumin in urine were measured with latex immunoassays as described previously\textsuperscript{26}. These methods involve agglutination of latex particles coated by specific antibodies provided by Dako Polska (Gdynia, Poland), and the results were verified against respective determinations by external laboratories. NAG activity in urine was measured using a commercially available colorimetric assay (Roche Diagnostics, Warsaw, Poland) according to the manufacturer’s instructions. Urine creatinine was measured according to the picrate method (Jaffe) using a commercially available assay (Aqua-Med, Lodz, Poland).

**Renal scintigraphy**

Dynamic renal imaging was carried out in the Department of Nuclear Medicine, Holycross Cancer Center, Kielce, Poland. The first renal scan was performed with \textsuperscript{99m}Tc-EC (tubular damage indicator), and two weeks later the same subjects underwent imaging with \textsuperscript{99m}Tc-DTPA (glomerular damage indicator). Both renal scintigraphies were performed in the same way. Prior to examination, the subjects were asked to drink ~0.5 l of water (7.0 ml/kg). \textsuperscript{99m}Tc-EC and \textsuperscript{99m}Tc-DTPA dynamic images were acquired with patients in the supine position and with the gamma camera head placed in a posterior view immediately after the intravenous administration of 370 MBq of the radiopharmaceutical. Data were acquired using a Multispect 2 or E-CAM gamma-camera (both from Siemens, Eschborn, Germany). The images were recorded in the energy window of 140 keV in 3 phases: vascular phase (0–2 minutes, image registration at 0.5 seconds intervals), filtration phase (2–5 minutes, image registration at 5 seconds intervals), excretion phase (5–25 minutes, image registration at 30 seconds intervals). The preinjection and postinjection syringes were counted on the camera, and counts for the postinjection syringe were corrected for decay and subtracted from the counts for the preinjection syringe to determine counts injected. Acquired data were processed using the ICON software (Siemens) and automatically normalized for age and body height and mass. In all subjects, clearances of \textsuperscript{99m}Tc-EC or \textsuperscript{99m}Tc-DTPA were estimated using the radiopharmaceutical administered for dynamic examination. The absolute value of \textsuperscript{99m}Tc-EC clearance was determined according to the method of Bubeck\textsuperscript{27}. The value of \textsuperscript{99m}Tc-DTPA clearance (GFR) was estimated without blood sampling according to the method of Gates\textsuperscript{28}.

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<th>Step</th>
<th>Lead</th>
<th>Cadmium</th>
<th>Gas flow rate (ml/min)</th>
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<td></td>
<td>Furnace temp (°C)</td>
<td>Time(s)</td>
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<td>1</td>
<td>110</td>
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Statistical analysis

Exploratory statistics were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium). The distribution of variables was assessed for normality using the Shapiro-Wilk test. Non-normally distributed parameters were analyzed after logarithmic transformation. The Student’s t-test (2-sided) or Welch’s t-test were used for comparison of means. Fisher’s exact test was used for analysis of categorical variables. Pearson correlation coefficients (r) were calculated on log-transformed data for the relationship between plasma lead concentrations and other variables. Stepwise multiple regression analysis was used to determine independent factors affecting dependent variables reflecting renal function. The following confounding variables were sequentially entered into the model: age, employment duration, smoking, systolic and diastolic blood pressure and cadmium concentration in urine. The results are expressed as percentages or means ± SD. Non-normally distributed variables are presented as geometric means (95% CI for the mean) back-transformed after logarithmic transformation. Differences or correlations with a p value <0.05 were considered significant.

Results

Characteristics of the studied groups

Characteristics of the exposed and control groups are shown in Table 2. Neither group differed significantly with respect to age, employment duration, and smoking habit. No significant differences were noted with respect to systolic and diastolic blood pressures.

Assessment of occupational exposure to air pollutants

Retrospective information regarding occupational exposure to air pollutants was obtained from the EHS department of the steel plant. In the years 1991–2000, the lead concentrations in the foundry working environment amounted up to 0.11 mg/m³ and exceeded the occupational exposure limit (OEL) of 0.05 mg/m³. Assuming that exposure to 0.1 µg/m³ lead in the ambient air produces an increase in the blood lead concentration of between 0.27 and 0.53 µg/dl[29–31], the blood lead levels of the foundrymen remained below or around 600 µg/l in this period. Due to changes in smelting technology, exposure to lead in the ambient air was reduced down to 0.04 mg/m³ from 2001 onwards, and the estimated blood lead concentration was 108–212 µg/l. In contrast to lead, exposure to other heavy metals including Cd, Fe, Mn, Cr and Ni, toxic gases such as CO and NO and total and respirable dust in the ambient air was below their respective OELs beginning in 1991. No information regarding the occupational exposure to air pollutants before 1991 was available.

At the time of the study (2008), the average blood lead concentrations were 145.8 (121.3–175.3) µg/l and 39.3 (35.1–44.1) µg/l in the exposed and control groups, respectively (p<0.001). By contrast, the urine excretion of Cd was comparable in both groups (1.5 ± 0.6 vs. 2.0 ± 0.8 µg/g creatinine; n.s.).

Determination of biochemical nephrotoxicity markers

To assess the potential effect of occupational exposure to lead on renal integrity and function, we first examined urine concentrations of several nephrotoxicity biomarkers in the exposed and control groups. As shown in Table 3, no significant differences were observed between the groups with respect to biomarkers reflecting tubular function and/or early tubular epithelial damage such as α1-M, β2-M, RBP and NAG activity. However, significantly higher concentrations of urine albumin, which reflects impaired glomerular function, were observed in the exposed group. Analysis of the distribution of nephrotoxicity markers in both examined groups revealed that 48% of foundrymen presented with urine albumin concentrations above the 90th percentile of the control group (p<0.001; see Table 4). By contrast, the percentage of individu-

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<th>Table 2. General characteristics of study subjects</th>
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<td><strong>Controls</strong> (n=40)</td>
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<td>Age</td>
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<td>Employment duration</td>
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<td>Smokers (&gt;10 cigarettes/day)</td>
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<td>Diastolic blood pressure</td>
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Values shown are means ± SD. Age and employment duration are given as years. Blood pressure is given as mmHg. For smokers, values represent % of examined population. Significance was determined by the Student’s t-test or Fischer’s exact test. n.s.: not significant.
Association between occupational exposure to lead and renal function

To more specifically address the influence of occupational exposure to lead on renal function, correlations between lead concentrations in blood and biochemical and scintigraphic indicators of renal function were examined in the combined groups. As shown in Table 5, there were significant correlations between albumin excretion and the blood lead concentrations, between the \(^{99m}\text{Tc-DTPA} \ T_{\text{max}}\) clearance and outflow index and between the \(^{99m}\text{Tc-EC} \ T_{\text{max}}\) and blood lead concentrations. Other biochemical or scintigraphic parameters reflecting renal function showed no significant correlations with blood lead concentrations. To examine associations between blood lead concentrations and each kidney outcome with adjustment for both kidney and lead confounders, a stepwise multiple linear regression analysis was performed with the blood lead concentration, age, employment duration, smoking, systolic and diastolic blood pressure and cadmium concentration in urine as explanatory variables. For albumin excretion, the best predictor was plasma lead concentration (\(\beta=0.55, p<0.01\)) followed by age (\(\beta=0.47, p<0.05\)) explaining, respectively, 30 and 21% of the albumin concentration in urine. For \(^{99m}\text{Tc-DTPA}\) clearance, the best predictor was plasma lead concentration (\(\beta=0.49, p<0.01\)) followed by diastolic pressure (\(\beta=-0.39, p=0.05\)) explaining, respectively, 24 and 15% of \(^{99m}\text{Tc-DTPA}\) clearance. No covariates were retained in models assessing the influence of the above exploratory variables on other renal function/injury parameters.

Discussion

It has been recognized for many years that occupational exposure to excessive lead concentrations in

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<th>Table 3. Biochemical and scintigraphic evaluation of renal function in study subjects</th>
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<td>Albumin (mg/g creatinine)</td>
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<td>(\beta)-microglobulin (µg/g creatinine)</td>
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<td>Retinol-binding protein (µg/g creatinine)</td>
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<td>N-acetyl-(\beta)-glucosaminidase (IU/g creatinine)</td>
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<td>(^{99m}\text{Tc-DTPA} \ T_{\text{max}}) (s)</td>
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<td>Clearance (ml/min)</td>
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<td>Outflow index (%)</td>
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<td>(^{99m}\text{Tc-EC} \ T_{\text{max}}) (s)</td>
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<td>Clearance (ml/min)</td>
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<td>Outflow index (%)</td>
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Values shown are geometric means (95% CI for the mean) back-transformed after logarithmic transformation. Significance was determined by the Student’s \(t\)-test or Welch’s \(t\)-test. n.s.: not significant.
ambient air may produce nephrotoxic effects such as interstitial nephritis or tubular damage and may ultimately result in renal failure. However, the role of low-level lead exposure as the cause of chronic kidney disease remains unsettled. Previous studies exploring renal effects of lead have frequently used parameters such as blood urea nitrogen, serum creatinine, or GFR for estimation of kidney function, which are inaccurate and do not allow for clearly discriminating between disturbances of glomerular and tubular functions. In addition, due to the great reserve capacity of the kidney, these measures of excretory functions may be normal despite considerable impairment of renal function. To circumvent these difficulties, we determined here for the first time $^{99mTc}$-DTPA and $^{99mTc}$-EC clearances in subjects chronically exposed to low to moderate lead concentrations in ambient air. The radioisotopic methods applied in the present study are more precise, enable direct estimation of glomerular and tubular clearance, and are often used as reference methods for the assessment of renal function\(^{32,33}\). Our results document two measurable aberrances of kidney function in the lead-exposed group. First, elevated $^{99mTc}$-DTPA clearance was observed in this group. Second, lead-exposed subjects excreted more urinary albumin as compared with controls. In addition,
both $^{99m}$Tc-DTPA clearance and albumin excretion were correlated with lead concentrations in blood of exposed subjects.

In major contrast to several previous studies, the urinary excretion of biomarkers reflecting tubular damage including $\alpha$M, $\beta$M, RBP and NAG activity was normal in subjects occupationally exposed to lead. The missing effect of low-level lead exposure on tubular function was further underscored by determination of $^{99m}$Tc-EC clearance, which directly reflects the excretory capacity of the nephron; the results were comparable between the exposed and control groups. However, the higher $^{99m}$Tc-DTPA clearance observed in the former group is highly suggestive of glomerular hyperfiltration, which may be a consequence of increased proximal tubular volume reabsorption. Glomerular hyperfiltration is a condition often encountered in various kidney pathologies (diabetes mellitus, polycystic kidney disease), where it precedes the deterioration of renal function and magnifies the risk of developing microalbuminuria\textsuperscript{33–36}. Other diseases and conditions such as sickle cell disease and hypertension, in which elevated glomerular filtration is present, are also associated with a higher risk for subsequent renal abnormalities including increased albumin excretion\textsuperscript{37, 38}. In this context, it is worth noticing that albumin excretion in five subjects (9%) in the lead-exposed group examined in this study exceeded the threshold of 24 mg/g creatinine, which defines microalbuminuria. Associations between increased GFR values estimated from creatinine clearance and higher lead exposure measures have been previously observed in subjects with long exposure histories and blood lead levels below 600 $\mu$g/l\textsuperscript{16, 17, 19, 39}. In addition, a positive association between GFR and blood lead concentration was reported in rodents exposed to 0.5% lead acetate in drinking water\textsuperscript{40}. Together with these previous studies, the present results suggest that the glomerular hyperfiltration may represent an early sign of renal dysfunction in prolonged low-level exposure to lead.

Several limitations of the present study have to be acknowledged. First, due to burdensome character of the radioisotope methods used for examination of glomerular and tubular functions, only small numbers of individuals could be included in the study, which limits its power. Second, the retrospective assessment of the occupational exposure to lead was mainly indirect, and the blood lead concentration in the period before the year 2000 was derived from the levels of this pollutant in the ambient air. Though blood lead concentrations estimated and measured at the time of the study were very close to each other, it cannot be entirely excluded that the levels of this metal in blood temporarily exceeded 600 $\mu$g/dl, especially in the early period of exposure. Third, though no significant difference in urine cadmium excretion was noted between the exposed and control groups at time of the study, limited retrospective information regarding the exposure to cadmium was available in the examined population. This may be of importance, as even low-level cadmium exposure seems to modulate lead-induced nephrotoxicity and higher urinary excretion of cadmium was found to be associated with increased creatinine clearance and GFR\textsuperscript{33–36}.

In conclusion, the present study revealed measurable alterations of renal function in low-level lead exposure and suggests that glomerular hyperfiltration may be an early indicator of functional impairments in subjects occupationally exposed to lead. Further prospective studies are necessary to clarify the clinical significance of this finding and to assess its utility in predicting nephrotoxicity in occupational exposure to lead.

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