Renal and immunological effects of occupational exposure to inorganic mercury

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Abstract

Seven parameters of renal dysfunction (urinary excretion of albumin, orosomucoid, β₂-microglobulin, N-acetyl-β-glucosaminidase (NAG), and copper; serum creatinine concentration, and relative clearance of β₂-microglobulin) were examined in a group of chloralkali workers exposed to mercury vapour (n = 89) and in an unexposed control group (n = 75). Serum concentrations of immunoglobulins (IgA, IgG, IgM) and autoantibodies towards glomeruli and other tissues were also determined. The parameters examined were compared between the two groups and related to different exposure parameters. In the chloralkali group median blood mercury concentration (B-Hg) was 55 nmol/l, serum mercury (S-Hg) 45 nmol/l, and urine mercury concentration (U-Hg) 14-3 nmol/mmol creatinine (25-4 µg/g creatinine). Corresponding concentrations for the control group were 15 nmol/l, 4 nmol/l, and 1-1 nmol/mmol creatinine (1-9 µg/g creatinine) respectively. None of the parameters of renal dysfunction differed significantly between the two groups, but there was a tendency to increased excretion of NAG in the exposed group compared with the controls. Also, a statistically significant relation existed between U-Hg and U-NAG (p < 0-001). Serum immunoglobulin concentrations did not differ between the groups, and serum titres of autoantibodies (including antiglomerular basement membrane and antilaminin antibodies) were low in both groups. Thus the results gave no evidence of glomerular damage or of a tubular reabsorption defect at the current relatively low exposures. The findings still indicate slight, dose related tubular cell damage in the mercury exposed group. There were no signs of a mercury induced effect on the immune system.

It is well known that inorganic mercury compounds may cause both glomerular and tubular damage. Grater, glomerular damage with nephrotic syndrome after exposure to mercury has been described in case reports and animal studies suggest that immunological mechanisms are involved in the aetiology of this glomerular injury. Increased prevalence of antilaminin antibodies has been reported among workers exposed to mercury in Belgium, but this finding was not confirmed in a later study.

The tubular damage is considered to result from toxic effects of mercury accumulated in the distal and middle portions of the proximal tubuli. If glomerular damage develops parallel to this, the resorption of filtered, protein bound mercury may cause pronounced tubular necrosis.

Increased urinary excretion of high molecular weight proteins, indicating glomerular dysfunction, has been related to occupational exposure to mercury in several studies. Tubular damage is often monitored by measurements of smaller urinary proteins such as β₂-microglobulin or retinol binding protein (RBP), and of tubular enzymes. Only a few studies of workers exposed to mercury have shown increased excretion of small proteins, suggesting tubular damage, whereas several authors have related the activities of certain lysosomal enzymes in urine to exposure to mercury.

The purpose of the present study was to compare renal function in a group of chloralkali workers exposed to mercury with that of an unexposed control group, and to study the relation between different dose indicators and the selected indicators of renal dysfunction. Also, a possible mercury induced humoral immune response was examined by determination of circulating immunoglobulins (IgA, IgG, IgM) and autoantibodies towards glomeruli and other tissues.
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Subjects
The study population was composed of a mercury exposed group of chloralkali workers from five plants, and a control group of industrial workers (not occupationally exposed to mercury) from two chemical industries, a paper works, and a sawmill. A total of 96 chloralkali workers and 80 unexposed workers were asked to take part in the study on a voluntary basis. Workers supposed to have high exposure to mercury were asked to participate first, as the object of the study was to detect renal damage induced by mercury. The exposed and control groups were comparable in age and type of work. Exposure to other heavy metals (for example, lead, cadmium), organic solvents, or excessive alcohol intake were criteria for exclusion.

The mercury exposed group comprised 89 workers (93% participation rate) with a mean age of 42.7 (SD 12.7) years. Their duration of exposure varied between one and 45 (mean 13.5 (SD 8.7)) years. The definitive control group consisted of 75 workers (94% participation rate) with mean age 43.6 (SD 12.5) years. For more details about the study population see Langworth et al.21

Among the exposed workers there were eight subjects with hypertension (four treated with diuretics and four treated with β-blocking agents), two with orally treated diabetes (type II diabetes), one with earlier history of renal stones, and one with suspected earlier pyelitis. Corresponding figures in the control group were: seven with hypertension (two treated with diuretics and five with β-blocking agents), one with orally treated type II diabetes, four with earlier renal stones, and one with suspected earlier pyelitis. In the statistical analyses the material was examined both in total and after elimination of individual subjects with the diseases mentioned.

Methods
All subjects underwent a routine clinical examination by a physician, including an interview focused on history of exposure and previous health state. In the chloralkali group, data from routine blood mercury controls during the past five years, and detailed information about the person’s work exposure were collected from each company’s health care unit. Data on smoking (smoker or not), intake of alcohol (average weekly intake of beer, wine, spirits) and consumption of fish (number of fish meals a week and type of fish eaten), were registered by a questionnaire and checked at the interview. Odontological state was recorded by a dentist. The total number of amalgam fillings, the number of amalgam surfaces of each filling (0–5), and the number of gold fillings were registered.

Blood and urine samples were collected on the same day as the physical examination. Samples for whole blood mercury analysis were collected in metal free, heparinised Venoject tubes (Terumo Europe NV, Leuven, Belgium) and serum samples for mercury analysis were collected in metal free Venoject tubes, which were centrifuged one hour after sampling to separate the blood cells. Morning urine samples were collected at home by each subject in 250 ml acid washed, polyethylene bottles and delivered to the company’s health care units where the urine was immediately examined with a test stick for pH, sugar, proteins, red blood cells, and bacteria (Boehringer Nephur-Test®, Mannheim, Germany). Urine samples with pH below 6 were tested for pH with a special test stick (Merck Spezialindikator pH 4.0–7.0, E Merck, Darmstadt, Germany). All samples were then poured into 12 ml metal free, plastic tubes, frozen, and stored at -20°C.

The selected indicators of renal dysfunction were: (a) urinary albumin concentration (U-albumin), (b) urinary orosomucoid concentration (U-orosomucoid), (c) urinary β₂-microglobulin concentration (U-β₂), (d) urinary N-acetyl-β-D-glucosaminidase activity (U-NAG), (e) urinary copper (U-Cu) concentration, (f) creatinine concentration in serum (S-creatinine), and (g) relative clearance of β₂-microglobulin.

Urinary albumin and orosomucoid concentrations were determined by zone immunoelectrophoresis assay (ZIA).22 Antibodies were from Dako, Copenhagen, Denmark, and Seronorm protein (Nycomed, Oslo, Norway) was used as standard. β₂-Microglobulin was quantified in urine and serum by radioimmunoassay (Phadebas β₂-microtest kit, Pharmacia, Uppsala, Sweden). Urine samples with pH below 5.6 were not analysed for β₂-microglobulin (n = 11 in the exposed group and n = 13 in the control group). After centrifugation and gel filtration of the urine samples on Sephadex G50 (Pharmacia, Sweden) to remove interference NAG activity in urine was determined colorimetrically.23 Creatinine concentrations in urine and serum were measured with Jaffe’s colorimetric method using picric acid and a reaction rate analyser (LKB 8600, Diagnostica, Boehringer-Mannheim GMBH, Germany). The copper concentration in urine was determined with electrothermal atomic absorption spectrophotometry (ETAAS) using the Perkin-Elmer Zeeman/3030 system, which comprised a microcomputer controlled spectrometer, a HGA-600 graphite furnace with an AC-Zeeman magnet, an AS-60 autosampler, and a PR-100 printer. Each sample was analysed in duplicate. In a sequence of 10 samples with a mean concentration of 24.6 μg/l the standard deviation (SD) was 1.0 μg/l, and the coefficient of variation (CV) was 4%. Relative clearance (Cl) of β₂-microglobulin (β₂) was calculated according to the formula:24

\[ \text{Cl } \beta_2 = \text{Cl creatinine (}\%\text{)} = 100 \times \frac{U-\beta_2 \times S\text{-creatinine}}{S-\beta_2 \times U\text{-creatinine}} \]
Serum concentrations of immunoglobulins (IgA, IgG, IgM) were determined by nephelometry and serum titres of autoantibodies to reticulin, smooth muscle, parietal cells, mitochondria, cell nuclei, and glomeruli were measured by an indirect immunofluorescence test. Specific antibodies to glomerular basement membrane antigen (anti-GBM) were determined by an "anti-Goodpasture" enzyme immunoassay from Biocarb Diagnostics AB, Lund, Sweden. Antilaminin antibodies were determined by an ELISA technique. Ninety six well Costar microwell titration plates were coated by laminin (Sigma Catalogue No L-2020) at a concentration of 10 μg/ml at 4°C overnight. After five washes in PBS (phosphate buffered saline), the plates were blocked for 20 hours by PBS containing 1% FCS (fetal calf serum) and 0.02% sodium azide. The plates were then washed three times in PBS and incubated for 20 hours at 4°C with a mouse monoclonal antilaminin antibody (Boehringer-Mannheim, Germany) or with serum diluted 1:100. After three washes in PBS the plates were incubated with alkaline phosphatase conjugated antibodies to human and mouse immunoglobulins respectively. The plates were finally washed three times and incubated with substrate (diethanolamine). The optical density was then read in a Bio TEK microplate EL 309 spectrophotometer at 405 nm.

Total mercury concentrations in whole blood (B-Hg), serum (S-Hg), and urine (U-Hg) were analysed in the laboratory of the Division of Medical Chemistry at the Swedish National Institute of Occupational Health. A modified version of the cold vapour atomic absorption spectrophotometry technique was used. For further details concerning quality control of the mercury analyses see Langworth et al.

The urinary excrections of mercury, proteins, NAG, and copper were adjusted for excretion of creatinine. Within the mercury exposed group the renal dysfunction parameters were related to five different exposure indicators: (1) current B-Hg, S-Hg, and U-Hg; (2) duration of exposure (number of work-years at the chloralkali plant); (3) intensity of exposure (low, medium, or high mercury exposure, based on the employees type of work and their expected exposure to mercury judged by one of the researchers and the company doctors); (4) consumption of fish (number of fish meals a week and type of fish); (5) amalgam burden (estimated as 0–5 amalgam surfaces for each tooth with amalgam fillings). In the control group the parameters of renal dysfunction were related to the exposure indicators 1, 4, and 5. Fish consumption and amalgam burden were included as indicators of background exposure to methylmercury and inorganic mercury respectively.

STATISTICAL ANALYSIS
Comparisons of the examined parameters (renal dysfunction parameters, immunoglobulins, and autoantibodies in serum) between the exposed and the control groups were made with Student's t test or the Mann-Whitney rank sum test (for skewed parameters). Dose-effect relations were studied with Pearson's correlation coefficient or with Spearman's rank correlation coefficient (for skewed parameters). In both groups the influence of age, smoking, and alcohol intake was examined by multiple regression and by analysis of variance (ANOVA).

The 90th percentiles of the parameters of renal dysfunction in the control group were regarded as upper normal and values above these among the exposed workers were considered as abnormal. The prevalence of abnormal values of the dysfunction parameters were then related to three concentrations of current U-Hg: (a) low = <10 nmol Hg/mmol creatinine; (b) middle = 10–25 nmol Hg/mmol creatinine; and (c) high = >25 nmol Hg/mmol creatinine.

The prevalence of abnormal parameters of renal function in the subgroups with low, middle, and high U-Hg were compared by χ² test or with Fisher's exact test. Minitab Data Analysis Software, release 7-2, Minitab Inc, USA, was used for all analyses except Fisher's test.

Results
In the occupationally exposed group median B-Hg was 55 (range 15–299) nmol/l, S-Hg 45 (1–255) nmol/l, and U-Hg 14·3 (0·3–46·9) nmol/mmol creatinine (25·4 (0·5–83·2) μg/g creatinine). These were significantly higher than in the control group where corresponding concentrations were 15 (1–63) nmol/l, 4 (1–25) nmol/l, and 1·1 (0·03–4·3) nmol/mmol creatinine (1·9 (0·05–7·6) μg/g creatinine) respectively. In the chloralkali group both B-Hg, S-Hg, and U-Hg were significantly related to estimated intensity of exposure but not to duration of exposure. In the control group the strongest predictor for B-Hg and S-Hg was fish consumption, whereas number of amalgam surfaces was the best predictor for U-Hg (see also Langworth et al.).

Smoking frequency was 44% (39/89) in the exposed group and 40% (30/75) in the control group. The estimated average weekly alcohol intake (centilitres of liquor) was 14 in the exposed group and 12 in the control group. In neither of the two groups did smoking or alcohol consumption influence the examined parameters.

Figure 1 describes the distribution of the parameters of renal dysfunction in the two groups. There was a tendency (not statistically significant) towards increased urinary NAG activity and decreased excretion of β₂-microglobulin in the mercury exposed group compared with the control group. The group difference in NAG excretion became slightly stronger, and statistically significant (p < 0·05), when workers with diabetes, hyperten-
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...and history of earlier renal disease were excluded from both groups. None of the other indicators (U-albumin, U-orosomucoid, U-Cu, S-creatinine, relative clearance of β2-microglobulin) differed significantly between the two groups. Serum concentration of β2-microglobulin in the exposed group tended to be low compared with controls (mean exposed group = 1.63 mg/l, range 0.8-2.6; mean control group = 1.78 mg/l, range 0.9-3.6; p = 0.10).

In the chloralkali group there were weak, but statistically significant, positive correlations between U-NAG and B-Hg (r = 0.29; p < 0.01), S-Hg (r = 0.26; p < 0.05), and U-Hg (r = 0.43; p < 0.001). Figure 2 shows the relation between U-Hg and U-NAG. A significantly higher prevalence of abnormal U-NAG (concentrations above the 90th percentile in the control group) was found in workers with high U-Hg compared with workers with low...
U-Hg. A similar tendency was noted for U-orosomucoid (fig 3).

None of the parameters of renal dysfunction was significantly correlated to duration or intensity of exposure. Weak, positive relations were found between age and both U-NAG and U-β₂-microglobulin.

In the control group, there were no significant relations between the parameters of exposure (current B-Hg, S-Hg, and U-Hg; fish consumption; amalgam burden) and the parameters of renal dysfunction. Age did not influence the parameters studied.

Serum concentrations of immunoglobulins (IgA, IgG, IgM) were normal in both groups (table 1) and we found no relation between immunoglobulin concentrations and the different parameters of exposure. The frequencies of raised titres of serum autoantibodies were low in both groups (table 2). Only one worker exposed to mercury had a weak, positive reaction in the anti GBM ELISA (13 units), and all the controls had negative reactions (<10 units). All responses in the antilaminin ELISA were considered as negative. Average antilaminin ELISA absorbance was 0.0362 (range 0-0.45) in the exposed group and 0.032 (range 0-0.43) in the control group.

Discussion

Animal studies, case reports, and experiences from highly exposed workers show that high exposure to inorganic mercury may cause renal damage. Less is known about renal effects after long term exposure to relatively low concentrations of inorganic mercury. Data on dose-response are scant, and many different indicators of renal damage have been used. Which is the most sensitive indicator of renal dysfunction remains to be identified.

It has been suggested that glomerular injury follows an immunological activation, with formation of autoantibodies towards the glomerular basement membrane. The role of mercury in the pathogenesis of this injury has been convincingly shown in animal experiments, and some case reports suggest that exposure to mercury may also lead to a glomerulonephritis and nephrotic syndrome in human subjects. Lauwers and coworkers reported an increased prevalence of antilaminin antibodies among workers exposed to mercury but this finding was not confirmed in a later study by the same researchers. Bencko et al described increased concentrations of serum proteins in workers exposed to mercury vapour compared with unexposed controls, but details concerning mercury concentrations in blood and urine were lacking in this report.

Increased excretion of serum proteins and of tubular enzymes are often used as indicators of renal injury, and the strategy of screening is discussed in two recent reviews. Buchet et al described increased urinary excretion of large proteins (albumin and transferrin) in chloralkali workers with U-Hg above 50 μg/g creatinine. The authors proposed a urinary biological threshold limit of 50 μg Hg/g creatinine (28.4 nmol/mmol creatinine), and...
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Table 1  Serum immunoglobulin concentrations in exposed and control groups

<table>
<thead>
<tr>
<th>Immunoglobulin concentrations (g/l)</th>
<th>Exposed (n = 89)</th>
<th>Controls (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>IgA</td>
<td>3.2</td>
<td>1.5</td>
</tr>
<tr>
<td>IgG</td>
<td>13.7</td>
<td>5.3</td>
</tr>
<tr>
<td>IgM</td>
<td>1.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

this proposal was supported in a later study in which both renal and central nervous system effects were examined. By contrast, Stonard et al. did not find any relation between exposure to mercury and the concentration of albumin in urine at a mean U-Hg of about 67 μg/g creatinine (38.1 nmol/mmol creatinine). Neither did Piikivi and Ruokonen find any increase in urinary albumin among a group of 60 Finnish chloralkali workers with a mean U-Hg of 10.1 nmol/mmol creatinine (17.8 μg/g creatinine).

Increased excretion of smaller proteins such as orosomucoid, β2-microglobulin, retinol binding protein (RBP), and of different enzymes, has been widely used as an indicator of tubular injury. Elinder et al. reported increased urinary orosomucoid with decreasing tubular reabsorption capacity, and increasing urinary β2-microglobulin among workers exposed to cadmium. A mercury related increase in urinary orosomucoid, besides increased excretion of large proteins, was reported by Buchet et al. The authors also described a slight increase of β2-microglobulin in plasma, without concomitant increase in urinary β2-microglobulin, and it was proposed that this finding indicated a small reduction of the glomerular filtration rate in the mercury exposed group. Stonard et al. described normal concentrations of β2-microglobulin in plasma, but lower β2-microglobulin excretion in the mercury exposed group than in the control group. This was interpreted as possible degradation of the protein in urine, enhanced by release of proteases from damaged tubular cells. The authors reported normal concentrations of orosomucoid in urine, and lack of relations between urinary β2-microglobulin, orosomucoid, and different exposure parameters.

In a study by Roels et al. slight tubular effects were detected as shown by an increased urinary excretion of RBP in workers exposed to mercury. Bernard and coworkers showed that increased excretion of RBP is a sensitive indicator of early tubular damage, and RBP was suggested to show a close correlation to β2-microglobulin. The authors also pointed out that RBP is more stable than β2-microglobulin in urine samples with low pH (<5.5).

The value of urinary enzymes as indicators of renal tubular damage has been discussed in several reports. In the screening for effects of mercury on tubules, the enzymes mostly used have been β-galactosidase, NAG, and γ-glutamyl transferase (γ-GT). The activity of β-galactosidase in urine has been related to exposure to mercury at U-Hg of about 50 μg/g creatinine or more by Buchet et al. and by Roels et al. Increased excretion of NAG and γ-GT is described by Stonard et al. at a mean U-Hg above 100 μg/g creatinine (56.8 nmol/mmol creatinine). Himeno et al. described increased urinary NAG activity at a U-Hg above 140 μg/g creatinine (79.5 nmol/mmol creatinine).

In the present study we analysed three urinary proteins (albumin, orosomucoid, and β2-microglobulin) of different molecular sizes, and one tubular lysosomal enzyme (NAG). The purpose was to discriminate between glomerular and tubular dysfunction. Measurements of β2-microglobulin and creatinine in both serum and urine made it possible to calculate the relative clearance of β2-microglobulin, which is considered as a sensitive measure of tubular function. Serum concentration of creatinine is often used as a screening tool for glomerular dysfunction in clinical practice. S-Creatinine does not, however, increase until the glomerular filtration rate is substantially reduced, and is therefore considered as an unsensitive indicator of glomerular damage. Increased excretion of copper and a positive relation between U-Cu and U-β2 have been found in workers exposed to cadmium, and U-Cu has been proposed as an indicator of tubular dysfunction.

Table 2  Serum autoantibody titres to different tissue antigens, determined by indirect immunofluorescence (number of subjects with titres ≥1/10)

<table>
<thead>
<tr>
<th>Tissue specificity</th>
<th>Serum titres</th>
<th>Exposed group (n=89)</th>
<th>Control group (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1/10</td>
<td>1/25</td>
</tr>
<tr>
<td>Reticulin</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parietal cells</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mitochondria</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ANA (nuclear)</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Glomeruli</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The finding of normal excretion of albumin in the mercury exposed group does not imply any effect of mercury on glomerular filtration of albumin at the current exposure levels and the lack of raised titres of serum autoantibodies to glomerular structures (both antiglomerular, anti-GBM and antilaminin) argues against the development of a mercury induced glomerulonephritis at the present degree of exposure to mercury. In earlier studies, increased proteinuria has been found at much higher exposure to mercury.
In accordance with Stongard et al. we found slightly decreased urinary concentrations of β₂-microglobulin in the exposed group compared with the control group, which may be explained by protein degradation due to release of proteases from injured tubular cells. This finding, together with relatively low serum concentrations of β₂-microglobulin in the exposed workers does not support the previously stated hypothesis of Buchet et al. The low excretion of β₂-microglobulin together with normal excretion of orosomucoid, copper, and normal relative clearance of β₂-microglobulin argues against a significant effect of mercury on the reabsorbing function of proximal tubules at the present levels of exposure.

Nevertheless, the slight increase in urinary NAG activity among the chloralkali workers combined with the positive relation between U-Hg and U-NAG indicates a slight tubular cell damage, probably due to exposure to mercury. The tendency to higher frequencies of increased U-NAG and U-orosomucoid among workers with high U-Hg (compared to those with low U-Hg; fig 3) strengthens this conclusion. The relation between U-orosomucoid and U-Hg was insignificant, however, and the linear relation between U-NAG and U-Hg was rather weak (fig 2). This is probably explained by the relatively low current U-Hg found in the exposed group (range 0–47 nmol/mmol creatinine = 0–83 μg/g creatinine). As stated, Stongard et al. reported raised excretion of NAG and γ-GT at U-Hg concentrations above 100 μg/g creatinine, and Himeno et al. described a rise in urinary NAG at U-Hg concentrations above 140 μg/g creatinine.

Both the group difference in U-NAG and the dose-effect relation between U-Hg and U-NAG in the exposed group became somewhat stronger when workers with hypertension, diabetes, and history of earlier renal disease were excluded. Several studies show that U-NAG may be raised in these conditions, so it seems reasonable to exclude workers with such diseases from the calculations (especially if the diseases are uncontrolled).

In the control group signs of glomerular or tubular dysfunction did not correlate with the different exposure indicators. The lack of correlation between amalgam burden and renal dysfunction implies no renal effect of dental amalgam, something that, based on animal experiments, has recently been suggested. Neither was exposure to methylmercury, estimated as weekly fish consumption, correlated with the parameters of renal dysfunction. Methylmercury is not known to cause renal effects, but background exposure to methylmercury (that is, contaminated fish) may disturb biological monitoring of exposure to inorganic mercury. Also, a demethylation of mercury has recently been reported in animal organs.

Our finding of normal concentrations of serum immunoglobulins in both groups contradicts the findings of Bencko et al. This, together with the normal titres of serum autoantibodies, argues against a mercury induced effect on human lymphocytes at the present exposure levels. The possible immunological effects on human subjects of exposure to mercury need further study.

In conclusion, we found no evidence of glomerular damage or defects in tubular reabsorption at the present low exposure to inorganic mercury. Nevertheless, the results indicate a slight tubular cell damage in the group occupationally exposed to mercury. The relation between U-NAG and current U-Hg together with the absence of influence (on U-NAG) from a cumulative exposure indicator such as duration of exposure suggest that this is predominantly an acute tubular effect, possibly of toxic aetiology. Altogether, this study, in accordance with earlier reports, shows that chronic low exposure to inorganic mercury can cause subclinical signs of nephrotoxicity. N-acetyl-β-D-glucosaminidase is established as one of the most sensitive indicators of proceeding renal tubular injury.

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