INFLUENCE OF OCCUPATIONAL EXPOSURE TO ORGANIC SOLVENTS ON KIDNEY FUNCTION

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Abstract
Exposure to nephrotoxic substances may cause renal tubular and glomerular dysfunction. The aim of the paper was to evaluate, based on literature reports, whether occupational exposure to organic solvents entails a risk of renal dysfunction. The results of the studies performed over the last twenty years are contradictory. In workers occupationally exposed to organic solvents, tubular, glomerular, or no effects were found. The lack of association between the renal effects and the intensity or duration of exposure was reported in most of the studies. It has been suggested that this can be attributed to an individual susceptibility. Available information points to a possibility of mild renal effects, but not to a serious influence on the kidney function at the current levels of occupational exposure to organic solvents. Biological monitoring of early effects can help identify individuals susceptible to nephrotoxicity of this group of chemicals.

Key words: Organic solvents, Kidney function, Occupational exposure

INTRODUCTION

Environmental and occupational exposure to nephrotoxic substances may cause renal tubular and glomerular impairments. The kidney is particularly vulnerable to these effects because of its structure and function. The kidney receives one-fifth of the resting cardiac output, 10% of which undergoes filtration at the glomerulus. This brings large amounts of solute to the glomerular and tubular compartments.

Physicians and toxicologists have different views on the nephrotoxicity of industrial chemicals. According to Wedeen [1] physicians tend to define a substance as hazardous only if the cause-effect relationship for the production of disease in human is clear. Toxicologists, on the other hand, accept the presence of even minute quantities of low molecular weight (LMW) proteins in urine as the evidence of a renal disease, because such findings warrant public health actions, i.e. reducing exposure. In fact, in the case of β2-microglobulin (β2-M), the LMW protein, the tubular reabsorption is 99.9% or more. Then, a relatively small decrease in the tubular reabsorptive capacity, from 99.9 to 99.0, will bring about a 10-fold increase in β2-M excretion in urine [2]. On the other hand, early detection of renal dysfunction resulting from occupational exposure to nephrotoxic chemicals is essential since this impairment may constitute the first step in a progressive loss of the renal function. As shown in the case of cadmium, removal from exposure at this early stage may allow a reversal of cellular changes or may at least hinder their further deterioration [3,4]. A reduction of occupational exposure limits, based on the results of biological monitoring of early renal effects, may prevent the occurrence of nephrotoxicity symptoms in the occupationally exposed populations.

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Nephrotoxicity of a chemical compound or its metabolites can be classified into two major categories: a direct, dose-dependent cytotoxicity and immunologically-mediated response, such as hypersensitivity, autoimmune reactions, and renal accumulation of circulating immune complexes [5]. Nephrotoxicity resulting from exposure to chemical compounds is usually confined to glomerular and tubular structures. Glomerular lesions often include high-molecular weight proteinuria, which may have different origin (loss of proteins from the urinary tract, defective reabsorption of filtered plasma proteins, nephron-loss proteinuria, increased glomerular permeability), decreased reserve glomerular filtration capacity, circulating anti-glomerular basement membrane antibodies, glomerular basement membrane antigens in serum and urine, and the presence of red cells, particularly red cell casts in urine sediment. Tubular toxicity is characterized by low molecular weight proteinuria, enzymuria, renal tubular antigens in urine, kallikrein and prostaglandin excretion, and other parameters, such as glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, hypouricemia, hypophosphatemia, and hypokalemia [6,7]. The nephrotoxic effects of organic solvents were reported after intoxication with different halogenated hydrocarbons, petroleum distillates, ethylene glycol ethers, and diethylene glycol [8–10]. Acute heavy exposure has also been suggested by case reports to result in Goodpasture’s syndrome [11,12]. Chronic exposure to solvents from repeated intentional heavy inhalation of toluene by “glue sniffers” is well known to lead to proximal and distal renal tubular disorders [13–17]. The results of some case-control studies provided evidence that chronic exposure to organic solvents led to the development of some types of glomerulonephritis. Daniell et al. [18] reviewed the case-control studies published before 1988. They found that despite methodologic limitations, seven of the nine studies showed statistically significant associations between solvent exposure and glomerulonephritis. The risk varied between 2.8 and 8.9. Based also on the results of case-control studies, Bell et al. [19], Porro et al. [20], and Stengel et al. [21] postulated that exposure to organic solvents may trigger the pathogenesis of non-systemic proliferative glomerulonephritis. On the other hand, Harrington et al. [22] reported that a history of solvent exposure had been found no more frequently in 50 biopsy-proven cases of glomerulonephritis than in 50 referent cases. The aim of this paper is to evaluate, on the basis of available literature data, whether exposure below the current occupational exposure limits entails a risk for renal toxicity. The terms “hydrocarbons”, “organic solvents” and “volatile organic chemicals” have all been used in the literature, reflecting very limited knowledge of the exact nature of mechanisms by which the renal damage is linked with this group of compounds. In this paper the term “organic solvents” will be used.

NEPHROTOXICITY OF ORGANIC SOLVENTS UNDER CONDITIONS OF OCCUPATIONAL EXPOSURE

From the early seventies of the last century, numerous reports have linked occupational exposure to organic solvents with both renal tubular and glomerular impairments. However, the chronic renal effects of exposure at workroom concentrations have not been adequately documented. In addition, little information was available at that time on the dose-response relationship. Having considered the quality of data on the level of exposure, the published reports can be divided into qualitative, semiquantitative and quantitative. Obviously the latter are of the highest value.

QUALITATIVE AND SEMIQUANTITATIVE DATA ON EXPOSURE

Askergren [23] investigated health effects of exposure to different organic solvents (styrene, toluene and xylene) in 101 males working in the plastic boat manufacturing industry (styrene exposure), photogravure printing (mainly toluene exposure) and paint manufacture (mainly xylene and toluene exposure). The controls were 39 non-exposed males. The exposed group was found to have a significantly higher rate of urinary excretion of erythrocytes and leucocytes than controls.
The aim of another study carried out by the same author [24] was to compare the glomerular and tubular type of protein excretion in 134 workers exposed to styrene, toluene, and xylene and in 48 persons not exposed to organic solvents. The workers were divided into three groups: those exposed to styrene, toluene and xylene–toluene. The background exposure to styrene was 20–100 mg/m³ and to toluene 300–400 mg/m³. No quantitative data on exposure were presented for the group exposed to toluene and xylene. The exposed groups excreted significantly larger quantities of albumin in urine than controls. No significant difference in urinary excretion of β₂-M was found between the groups. According to the authors the findings confirmed a possible association between exposure to organic solvents and glomerular disease.

Hashimoto et al. [25] investigated a relationship between exposure to organic solvents and increased urinary cellular sediment. They conducted a cross-sectional study of 215 newspaper pressroom workers exposed to seven different solvents and lubricants. Thirty-two persons were surveyed as referents. The concentrations of compounds identified in the air (total naphtas, glycol ethers) were low, but according to the authors, there was a considerable potential for dermal exposure. At the time of the study, a high prevalence of solvent-related dermatitis was noted among the workers. Therefore, the number of solvents used by a particular worker rather than the solvent concentration in the air was considered an independent variable. The authors found a dose-related relationship between the number of solvents used by worker groups and the prevalence of increased leukocyturia alone or in urinary cellular sediment (erythrocyturia and/or leukocyturia). In 16% of pressmen, but not in controls, low-grade albuminuria was detected by dipstick.

Hotz et al. [26–28] carried out studies on exposure to organic solvents in various occupational and non-occupational activities. Solvent exposure was assessed with a questionnaire and so called intensity factors. In this method, the exposure duration is assessed and then multiplied by an independently determined intensity factor. The units are years weighted by the exposure intensity factor. Heavy exposure (intensity factor 2) comprised such activities as occupational house painting indoors, industrial spray painting without protecting devices, floor laying and impregnating, production of paint, production of glue, polyester resin application involving intensive contact with styrene, tank cleaning, and paint stripping with organic solvents. Moderate exposure (intensity factor 1) referred to non-occupational house painting indoors, spray painting with protective devices, industrial degreasing of metal, printing work, occupational gluing, anesthetic work, dry cleaning, use of hair sprayers, use of pesticides, polyester resin applications with low exposure to styrene. Slight exposure (intensity factor 0.5) covered outdoor painting, motor repair, handling of petrol fuels, tank cleaning with protective devices, hobby gluing, exposure to exhaust fumes outdoors.

In the first of these studies [26] the authors found a weak but statistically significant correlation between exposure score and β-N-acetyl-D-glucosaminidase (NAG) activity or erythrocyturia (r = 0.21 and 0.12, respectively). In the second study [27], the excretion of albumin, retinol binding protein (RBP), β₂-M, and NAG activity was studied, but there was no clear-cut relationship between exposure scores and the observed effects. The authors hypothesized that people with potential kidney damage of non-occupational origin, such as hypertension could be at a higher risk for developing subclinical signs of kidney damage than their healthy counterparts. They also concluded that albumin excretion rate, NAG activity, and RBP concentration in urine are among the most valuable indices in field studies on the nephrotoxicity of occupational organic solvents exposure. In the third study [28], the authors found an interaction between hypertension and cumulated hippuric acid excretion in urine in a population of printers exposed to toluene. This interaction was significantly associated with abnormal proteinuria, increased serum laminin concentration, albumin excretion rate, and NAG activity in urine. The findings of all the three studies made the authors conclude that occupational exposure to organic solvents is a non-specific factor that may promote an impairment of the renal function.

In the reports published by a research team of the Royal Liverpool University Hospital, UK, the evaluation of cu-
mulated exposure to organic solvents was based on a questionnaire study. Yaqoob et al. [29] studied renal glomerular and tubular abnormalities in three groups of healthy men working in different departments of a car factory. Group 1 comprised 112 paint sprayers, group 2–101 workers exposed to petroleum-based mineral oils, and group 3–92 automated press operators with minimal background exposure to lubricants. Group 1 had a significantly higher prevalence of elevated serum creatinine than the other two groups and a higher prevalence of abnormal urinary total protein, NAG, γ-glutamyl transferase (γ-GT), and leucine-aminopeptidase (LAP) excretion than groups 2 and 3. Group 2 had normal serum creatinine, but a significantly higher prevalence of abnormal urinary total protein, transferrine, RBP, NAG, and LAP excretion than group 3. Stevenson et al. [30] investigated basement-membrane-associated mechanisms in renal disease induced by organic solvents. Three groups of workers, similar to those described above, were examined. Group 1 consisted of 111 paint sprayers, group 2 of 100 transmission shop workers and group 3 of 92 automated press operators. Group 4 (controls) included 108 males with no known occupational exposure to organic solvents. Group 1 had a significantly greater proportion of subjects with high levels of both anti-laminin antibodies and soluble E-selectin. In group 2, significantly more subjects had elevated levels of anti-glomerular basement membrane (AGBM) antibodies, laminin (LAM), and soluble E-selectin. The mean levels of soluble E-selectin were increased in groups 1 and 2. In a small, but a significant proportion of these workers, alterations to basement membranes, resulting in autoantibody production, and to overlying vascular endothelial cells could be noted.

QUANTITATIVE DATA ON EXPOSURE
Mutti et al. [31] estimated proteinuria, albuminuria, urinary β-glucuronidase (β-GLU) and serum creatinine in 182 workers exposed to organic solvents in four shoe factories, 30 workers with past exposure and 80 control subjects. In most cases the total concentration of n-hexane, cyclohexane, methyl-ethyl ketone, ethyl acetate, and acetone exceeded the threshold limit value (TLV) for the mixture. In the 1980s, TLVs of many substances were higher than the current values, e.g., the TLV for n-hexane was 360 mg/m³ compared to the current value of 176 mg/m³ [32]. Proteinuria was significantly higher in the exposed group than in controls or in the group of ex-workers. Albuminuria or serum creatinine remained within normal limits. These findings imply that mild and presumably reversible impairment of the renal functions may occur as a consequence of exposure to C₅–C₇ aliphatic hydrocarbon mixture and its localization is tubular rather than glomerular. Franchini et al. [33] carried out a cross-sectional study of workers significantly exposed to a mixture of alicyclic and aliphatic C₅–C₇ hydrocarbons, styrene, a mixture composed mostly of toluene and xylene, and chlorinated hydrocarbons. The study involved four groups of workers (dry-cleaners, painters, laminators, and shoemakers) and two control groups. In the first three groups of workers the assessment of exposure was based on biological monitoring. The first group (n = 57) was exposed to perchloroethylene (PERC) for 13.9 years on average at the mean concentration of about 70 mg/m³. The second group of 118 painters was exposed to benzene homologues. The concentration of toluene in the air, based on the determination of urinary hippuric acid, amounted to about 90 mg/m³. The third group (n = 51) was exposed to styrene and the calculated air concentration level amounted to approximately 200 mg/m³. The exposure of the last group (n = 212) was the same as that presented in a previous paper [31]. Total proteinuria was found to be significantly increased in workers exposed to C₅–C₇ hydrocarbons as compared to the reference and the other groups of exposed workers. No differences between any groups were found for albuminuria. The group of dry-cleaners exposed to PERC and of painters exposed to toluene and xylene showed a statistically significant increase in urinary excretion of β-GLU compared to both reference groups. The dry-cleaners and laminators had lysozymuria significantly higher than both reference groups.

According to the authors, the study provided some evidence of kidney damage in workers occupationally exposed to organic solvents. This effect seems to be very
weak and tubular, rather than glomerular, as suggested by the above mentioned case-referent studies.

Viau et al. [34] investigated sensitive biochemical and immunological markers of kidney function in 53 oil refinery workers. The exposure was found to be low. The total time weighted average (TWA) concentration of organic solvents varied from 1 to 156 mg/m³ for individual workers. The concentrations of toluene, n-hexane, n-butane, and n-pentane were in the range of about 1% or below current TLVs. No difference was found in the urinary tubular parameters and glomerular filtration rate between the exposed and control groups. The circulating immune complexes were also identical in both groups. The mean albuminuria was slightly higher in the exposed workers (p < 0.005). To conclude, the chronic low-level organic solvent exposure did not lead to clinically significant renal abnormalities.

Urinary excretion of total protein and β₂-M in 104 male workers exposed to trichloroethylene (TRI) was evaluated by Nagaya et al. [35]. The workers were exposed to TRI probably at the level of approximately 80 mg/m³ (current TLV–TWA: 269 mg/m³) [32]. In the exposed workers the total urinary protein level, rather than urinary β₂-M, was slightly higher than in controls. These results suggested that the adverse effect of trichloroethylene on the kidney at this level of occupational exposure was glomerular rather than tubular and very mild.

Biochemical markers of kidney damage were examined in 37 female workers exposed to an average concentration of 225 mg/m³ styrene [36]. This concentration was about 2.5 times higher than the current TLV–TWA of 85 mg/m³ [32]. The concentration of mandelic acid in urine was 759 mg/g creatinine on the average, which confirms the estimated level of exposure. The mean duration of worker’s employment of the subjects was 11 years. No difference was found between the study and control groups with respect to the urinary excretion of albumin, β₂-M, RBP, total proteins, glucose, lysozyme, LDH, and NAG. These results indicate that styrene exposure at concentrations of about 200 mg/m³ does not entail any detectable risk for the renal function. The negative results were obtained by these authors also in the case of occupational exposure to PERC and a mixture of organic solvents. Vyskocil et al. [37] carried out a study on biochemical markers of kidney damage in 16 female workers with chronic exposure to PERC. The time-weighted average exposure to PERC amounted to 157 mg/m³. The urinary excretion of lysozyme was higher in the exposed group than in controls. No difference was found in the urinary excretion of albumin, β₂-M, LDH, total proteins or glucose. The prevalence of abnormal values of biochemical parameters in the exposed group did not differ from that found in the control group. The findings suggested that chronic exposure to PERC at the level close to the current TLV-TWA of 170 mg/m³ [32] should not lead to renal damage. In another investigation [38] the study group consisted of 59 workers exposed to petroleum-naphtha and toluene in a shoe factory. The TWA concentrations of petroleum naphtha, toluene, and ethyl acetate were 1619, 81, and 160 mg/m³, respectively. No significant changes were noted in measurements of the urinary excretion of total protein, β₂-M, RBP, albumin, transferrine, lysozome or LDH. The only parameter that differed significantly was the urinary activity of NAG. The authors concluded that the long-term moderate exposure to these solvents did not evoke significant risk for the development of nephrotoxicity.

Ng et al. [39] measured urinary excretion of albumin and RBP in 45 paint workers exposed mainly to toluene. The air concentrations of toluene were below 376 mg/m³. Hippuric acid and o-cresol excretion in urine were determined to assess the exposure level. In about 70% of the exposed workers, urine concentration of o-cresol was higher than the current biological exposure indices (BEI) value of 0.5 mg/l [32]. A significantly higher mean RBP concentration in urine (150 µg/g creatinine) and increased prevalence (33%) of values above the cut-off level were found as compared to the results for matched controls (88 µg/g creatinine and 4.4%, respectively). No significant difference in urinary albumin concentration was noted between the two groups. Urine concentrations of RBP correlated (r = 0.399, p < 0.006) with that of o-cresol. The findings of this study indicate a dose-dependent early tubular effects due to toluene exposure.

In a collaborative European study, Mutti et al. [40] assessed the renal effects of occupational exposure to PERC in dry-
cleaners as compared with matched controls. Exposure levels ranged from trace amounts up to 580 mg/m³. Blood PERC concentrations were measured as well. The median values of PERC in air and blood were about 100 mg/m³ and 143 μg/l, respectively. The median concentration in the air was lower than the current TLV-TWA of 170 mg/m³ [32]. In this study, a large number of markers of early kidney dysfunction was determined (19 in urine and 4 in serum). PERC-exposed workers had a higher rate of excretion of high-molecular weight proteins (albumin, transferrin), brush border antigens (BBA, BB50, HF5), fibronectin (FNU), and tissue non-specific alkaline phosphatase (TNAP). The higher excretion of glycosaminoglycans (GAGs) and Tamm-Horsfall glycoprotein (THG) also approached statistical significance. The level of serum AGBM antibodies and laminin fragments (LAM) was significantly higher in PERC-exposed workers. Serum creatinine and β₂-M overlapped in the examined groups, thus excluding major impairments of the renal function.

Both the exposed and control groups showed a similar frequency of abnormally high levels (above the cut-off levels) of FNU, TNAP, BB50, and serum AGBM antibodies, whereas the proportion of subjects with low molecular weight proteinuria (RBP, β₂-M) and increased urinary IgG, GAGs, and THG was significantly higher in the PERC-exposed workers than in controls. Correlation analysis did not reveal significant associations between independent variables and renal markers. In PERC-exposed subjects, high molecular weight proteinuria was frequently associated with the markers of tubular dysfunction, i.e. with low molecular weight proteinuria and/or urinary excretion of tubular antigens (17/50 vs. 1/50 in controls, p < 0.0001). This study, based on a battery of markers of renal damage and/or dysfunction, confirmed early renal effects among workers occupationally exposed to organic solvents. Diffuse abnormalities occurred at the glomerular and tubular proximal and distal levels. According to the authors, these subtle abnormalities may represent an early stage of clinically silent but potentially progressive renal disease.

The study carried out by Rasmussen at al. [41] concerned 99 workers engaged in metal degreasing with TRI or fluorocarbon (CFC 113). A cumulative exposure index was calculated using the number of working hours per week, multiplied by the years of exposure, and multiplied by 45 working weeks per year. Following this estimation, the study subjects were divided into four groups: group 1 (reference group) with cumulative exposure of less than 1 year, group 2, 1–2.8 years, group 3, 2.9–6.7 years, and group 4, 6.8–35.6 years. In the highest exposure group, the mean concentration of trichloroacetic acid (TCA) in urine was 7.7 mg/l, with the maximum TCA concentration of 16 mg/l. Historical data indicated a fairly constant exposure level corresponding to about 40–60 mg TCA/l of urine from the mid 1950s to the mid 1970s. The present BEI amounts to 100 mg/g creatinine [32]. The mean urine concentration of NAG in the study group was 53.6 μg/g creatinine (reference values 30–60 μg/g creatinine). Urinary NAG excretion indicated a significant dose-response relationship (p < 0.05) between the cumulative exposure to all organic solvents and urine concentrations of NAG in the respective groups. However, when age was included as a confounder in the multiple regression analysis, the relationship between solvent exposure and NAG excretion became insignificant. Verplanke et al. [42,43] studied the effects of occupational exposure to styrene and PERC on the kidney. In one study [42], 10 styrene exposed workers (mean employment time 12.6 years) and 15 non-exposed workers were examined. Each participant collected multiple overnight and end-of-shift urine samples. The total of urinary concentrations of mandelic acid and phenylglyoxalic acid (MAP) was determined. The median weekly concentration of MAP in urine samples collected overnight was 175 mg/g creatinine (72–496 mg/g creatinine). According to Guillemin and Berode [44], the concentration of 330 mg MAP/g creatinine corresponds to an 8-h time-weighted average exposure to 213 mg/m³ styrene. Based on this assumption, the authors estimated that the median weekly exposure to styrene in the exposed group was 113 mg/m³ (21–405 mg/m³). The estimated 8-h TWA exposure to styrene, calculated from every individual MAP value, varied from 21 to 405 mg/m³. The current TLV-TWA amounts to 85 mg/m³ [32]. A number of urinary parameters, including alanine aminopeptidase (AAP), β-galactosidase (β-GAL), NAG, RBP, and albumin were determined to
assess the effects on renal functions. The concentrations of RBP in overnight urine samples and of albumin in end-of-shift samples were found to be higher in the exposed group (p < 0.10). No differences between the exposed and control groups were found for any other renal-effect parameter examined. RBP in overnight urine samples and albumin in end-of-shift samples showed a borderline association with the dose at the significance levels of p < 0.01. The tubular effects appeared to contradict each other because a negative correlation between NAG and MAP in overnight urine samples (p < 0.004) could be observed. The findings were of no biological or physiological significance because all the NAG and RPB concentrations were low and below the reference limit of the laboratory (7 U/g creatinine and 200 μg/g creatinine, respectively) and only two urine albumine concentrations were above the upper reference limit value (20 mg/g creatinine).

In the other study, Verplanke et al. [43] assessed the effects of PERC exposure on the kidneys in 82 exposed and 19 non-exposed workers at four dry-cleaning shops in the Netherlands. The level of exposure was assessed by determining PERC in alveolar air samples collected on a Tuesday morning, before the workshift. The geometric mean (GM) concentration of PERC in alveolar air of the exposed group was 8.4 mg/m³ (2.2–44.6 mg/m³). This value corresponds to the mean 8-h TWA exposure of 7.9 mg/m³ (1–221 mg/m³). PERC was not detected in the alveolar air of the non-exposed participants. The estimated GM 8-h TWA exposure to PERC was much lower than the current TLV-TWA of 170 mg/m³ [32]. Chronic dose index (CDI) was estimated from the data on the current PERC dose and the work history of individual subjects. The mean CDI in the exposed group was 400 months • mg/m³ (12–4882 months • m³). Urine and serum samples were used to determine the renal-effect parameters. Effects on tubules were assessed on the basis of NAG, β-GAL, AAP, and RBP determinations in urine. Albumin concentration in urine used as an indicator in monitoring of early effects on the glomeruli did not differ between exposed and non-exposed groups. The same observation was made concerning the mean activities of urinary enzymes. The GM concentration of RBP in urine was higher in the exposed group (ratio = 1.81; p < 0.009). None of the renal-effect parameters correlated with the dose indices. The authors concluded that occupational exposure to PERC may cause minor changes in the tubular RBP at exposure level below 240 mg/m³.

**CONCLUSIONS**

The results of the studies, which contained quantitative information data on the levels of exposure based on the environmental or biological monitoring are summarized in Table 1. Contrary to the results of the case-control studies, where the cases were selected from patients suffering from glomerulonephritis, in workers occupationally exposed to organic solvents both tubular and glomerular effects were found. Contradictory results were obtained even when the study groups were exposed to the same solvents and similar markers of effects were determined in biological material. For example, in the same styrene-exposed population, Verplanke et al. [42] found out that the NAG activity decreased and RBP concentration increased with increasing level of exposure. The excretion of selected markers of kidney dysfunction could be occasionally lower in the exposed groups than in controls [36,43].

A common finding was the lack of association between renal damage and magnitude or duration of exposure with exception of the correlation between urinary RBP and o cresol [39], and the exposure related trend of urinary cellular sediment and albuminuria among newspaper workers exposed to solvent mixtures [25]. The last paper was not included in the table because it reported the semi-quantitative assessment of exposure. The prevailing absence of the dose-effect and dose-response relationships can be explained by inadequate evaluation of exposure at the group levels and individual susceptibility to organic solvents. Mutti et al. [40] suggested that in susceptible individuals, peak exposures may lead to autoimmune glomerular diseases. Hotz et al. [27] hypothesized that people with a possible kidney damage of non-occupational origin such as hypertension could be at a higher risk for developing subclinical signs of kidney damage than their healthy counterparts.

The findings of the studies summarized in Table 1 imply the possibility of mild early effects rather than of serious influ-
Table 1. Summary of the results of studies on the effects of occupational exposure to organic solvents on the renal effects parameters (quantitative data on exposure)

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Substances</th>
<th>Approximate concentration in the air (mg/m³)</th>
<th>Biological parameters measured</th>
<th>Effects</th>
<th>Site of effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>Styrene</td>
<td>20–100</td>
<td>Urine; albumin, β₂-M</td>
<td>Albumin concentration increased in the exposed</td>
<td>G</td>
<td>[24]</td>
</tr>
<tr>
<td>42</td>
<td>Mainly toluene</td>
<td>300–400*</td>
<td></td>
<td>No significant difference in β₂-M excretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
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<td></td>
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<td>182</td>
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<tr>
<td>80</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>PERC</td>
<td>70</td>
<td>Urine: total proteins, albumin, lysozyme, creatinine Serum: creatinine</td>
<td>Total proteinuria increased in workers exposed to C₅–C₇ hydrocarbons</td>
<td>Rather</td>
<td>[33]</td>
</tr>
<tr>
<td>118</td>
<td>Benzene homologues (toluene)</td>
<td>90</td>
<td></td>
<td>Increase of excretion of β-GLU in exposed to PERC and benzene homologues and increased lysisomuria in exposed to styrene</td>
<td>T</td>
<td>[31]</td>
</tr>
<tr>
<td>50</td>
<td>Styrene</td>
<td>200*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>212</td>
<td>Shoe factories [31]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>161</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Oil refinery workers. Total hydrocarbons concentration</td>
<td>1–156</td>
<td>Urine: NAG, β₂-M, RBP, albumin, renal antigen Serum: β₂-M</td>
<td>The mean albumine and renal antigen slightly higher in the exposed group</td>
<td>G</td>
<td>[34]</td>
</tr>
<tr>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td>No clinically significant renal abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>Control</td>
<td></td>
<td>Urine: total protein β₂-M</td>
<td>Total protein concentrations slightly higher than in control group</td>
<td>G</td>
<td>[35]</td>
</tr>
<tr>
<td>102</td>
<td>Trichloroethylene</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Control</td>
<td></td>
<td>Urine: β₂-M, RBP, albumin, NAG, lysozyme, LDH, total proteins</td>
<td>No effects</td>
<td></td>
<td>[36]</td>
</tr>
<tr>
<td>35</td>
<td>Styrene</td>
<td>225*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Control</td>
<td></td>
<td>Urine: β₂-M, albumin, LDH, total proteins, glucose, lysozyme</td>
<td>Increased excretion of lysozyme Prevalence of abnormal values did not differ from observed in the control group No detectable risk for the renal function</td>
<td>T</td>
<td>[37]</td>
</tr>
<tr>
<td>13</td>
<td>PERC</td>
<td>157</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Control</td>
<td></td>
<td>Urine: β₂-M, RBP, LDH, lysozyme, NAG, total proteins, transferin, albumin</td>
<td>Increased excretion of NAG No significant risk for the development of nephrotoxicity</td>
<td>T</td>
<td>[38]</td>
</tr>
<tr>
<td>59</td>
<td>Petroleum naphtha Toluene Ethyl acetate</td>
<td>1619* &lt;376* o-cresol in urine (present BEI 0.5 mg/g creatinine, BEI &lt; 12 persons BEI &gt; 33 persons)</td>
<td>Urine: RBP Albumin, RBP</td>
<td>Significantly increased excretion of RBP in urine</td>
<td>T</td>
<td>[39]</td>
</tr>
<tr>
<td>45</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Mainly toluene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Control</td>
<td></td>
<td>Urine: 9 markers (high and low molecular weight proteins, kidney-derived antigens and enzymes, and prostanoids) Serum: β₂-M, creatinine, laminin fragments, AGBM</td>
<td>A canonical function based on 23 variables correctly classified 93% of individuals as either PERC-exposed or controls High molecular weight proteinuria was frequently associated with markers of tabular alterations and/or urinary excretion of tubular antigens</td>
<td>TG</td>
<td>[40]</td>
</tr>
</tbody>
</table>
ence of occupational exposure to organic solvents on the kidney function at the air concentrations below the current occupational exposure limits. However, these early effects may represent a clinically silent but potentially progressive renal disease in sensitive individuals. Therefore, in addition to exposure assessment, the biomonitoring of early effects of kidney dysfunction, via determinations of albumin excretion rate, NAG activity and RBP concentration should be considered in persons occupationally exposed to organic solvents as this can be helpful in identifying susceptible individuals.

REFERENCES

32. ACGIH. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati (OH): American Conference of Governmental Industrial Hygienists; 2003.