Industrial Solvents and Kidney Disease

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Scientific literature addressing the association of industrial exposures to solvents with glomerular kidney disease is reviewed. The role of the practicing physician in taking an occupational history of exposures to solvents in every case of glomerulonephritis is emphasized. Based on case studies and epidemiologic findings, it is highly probable that exposures to industrial solvents should be considered as a factor in the causation of kidney disease. The need for more frequent reporting is discussed. Key words: industrial solvents; kidney disease; glomerulonephritis.

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Industrial solvents (hydrocarbons) are used extensively in industry, as well as daily life. Hydrocarbons in common use include aliphatic aromatics, chlorinated, and napthenes. Workers routinely exposed to such solvents include mechanics, painters, printers, parts fabricators, auto parts cleaners, degreasers, pharmacists, research technicians, police officers, and firefighters. Studies in experimental animals, case reports, case studies, and epidemiologic studies have documented the acute and chronic effects of solvents on the kidney. This article reviews the scientific literature on the association of solvent exposures with chronic glomerular kidney disease.

ABSORPTION, DISTRIBUTION, AND METABOLISM

Solvents are absorbed into the human body through several routes, including 1) inhalation through the lungs, 2) absorption through the skin, and 3) ingestion (in rare cases). The main route of absorption is pulmonary, and this depends on several factors, including the frequency of breathing, diffusion of solvent vapors across the alveolar membrane, partial pressures of solvent vapor in inspired air and blood, solubility of the solvent in blood as the result of the blood–air partition coefficient, and blood flow through the lungs.¹–³ Once in the circulation, 25% of the cardiac output, which is about 1,200 mL of blood per minute, passes through the kidneys. This amount of blood passing through the kidney and carrying solvents (from inhalation, skin absorption, or ingestion) has effects on the kidney that are of clinical significance.

Skin absorption, the second most important route for solvent entry into the body, is at times much more toxic than inhalation. Absorption of organic solvent vapors by inhalation at the threshold limit value is insignificant and is less than 2% of the amount absorbed through the skin under the same exposure conditions.³ In contrast, solvents may be absorbed through the skin in significant amounts even below the threshold limit value.³ Factors that affect cutaneous absorption of solvents include the composition of the skin, whether the skin is healthy or not (absorption is increased when the cutaneous cellular membrane is reduced), and the lipid solubility of the solvent. It is important to recognize that a mixture of solvents is more readily absorbed via the skin than a single solvent.

The gastrointestinal tract is not commonly a significant route of absorption. Solvents absorbed via the gastrointestinal tract are removed immediately by the liver through the first-pass metabolism. Only if the quantity of solvent ingested exceeds the capacity of the liver to metabolize it is the gastrointestinal tract route significant.⁴–⁶

The distribution of an organic solvent in the human body depends upon its partial pressure in the arterial blood and its solubility in tissue, as well as the rate of blood flow through the tissue.⁷ Alcohols are metabolized via alcohol dehydrogenase, whereas other organic solvents are mainly metabolized by cytochrome P-450–dependent enzymes in the liver, kidneys, lungs, gastrointestinal tract, gonads, adrenal cortex, and other body organ tissues. (The metabolism of solvents is described extensively elsewhere.⁸,⁹) The metabolites of organic solvents are eliminated via the kidneys through urine excretion and, to some extent, by exhalation of the unchanged original solvent. Commonly the parent solvent is eliminated by the kidneys, and this accounts for less than 1% of the amount absorbed. Metabolites are the main source of excretion of the absorbed parent solvent.

Some solvents enhance the metabolism of others, while others inhibit metabolism and thereby increase solvents levels in the blood and reduce elimination time. Exposures to chemicals in general and to solvents in particular are often exposures to mixtures rather than to single agents. This aspect is important for risk assessment. More often than not, the effects of a sol-
vent mixture are additive. Therefore, even at a low level of exposure to a mixture, the toxicity resulting from the additive effect of several solvents will exceed the toxicity of a single solvent.

**EXPERIMENTAL ANIMAL STUDIES**

The toxic effects of organic solvents on the kidneys have been studied in several experimental species, especially mice and rats. Damage to the kidney has been shown in these experimental animals in the form of acute damage to various parts of the nephron, especially the tubules. This has usually been described as tubular degeneration with regenerative epithelium, deposits of mineral crystals and of intralobular proteins, and interstitial inflammation. Several investigators have shown glomerular damage in experimental animals and have suggested that long-term solvent exposure alters the immune system and leads to the glomerulopathy with mesangial IgA deposits.

**CASE REPORTS**

An early description of the association of chronic renal disease with solvent exposure appeared in case reports summarized by Churchill et al. They reported cases of Goodpasture’s syndrome in 15 adults, epimembranous glomerulonephritis in five adults, and subacute proliferative glomerulonephritis in one adult. The hydrocarbons these patients had been exposed to were solvents in 12 cases, gasoline in four, gasoline-based paint in three, and jet fuel, mineral turpentine, and unspecified in one each. These case reports, summarized elsewhere, are listed in Table 1.

**CASE–CONTROL STUDIES**

Various case–control studies have examined the role of organic solvent exposure in a population of patients with glomerulonephritis. These are listed in Table 2. Lagrue et al. showed a significantly increased risk factor for glomerulonephritis with exposure to solvents of 4.9. That this increased risk of glomerulonephritis follows a dose–response relationship was shown by Ravnskov et al., who reported risk factors of 3.9 and 2.8 with a dose–response ratio. Nuys et al. examined 272 patients with chronic renal failure and assessed several occupational exposures, among which were hydrocarbons. The risk factor for chronic kidney disease in the form of renal failure in patients exposed to solvents was 5.45. Askergren et al. examined kidney function in patients exposed to various organic solvents, specifically excretion of red blood cells in the urine in 101 patients exposed to solvents as compared with 39 non-exposed controls. Those who were exposed to organic solvents excreted significantly more cells than the unexposed controls. These studies evidence the role of organic solvent exposure in the development of glomerular damage, since excretion of red blood cells is a result of glomerular damage.

**TABLE 1. Case Reports of Hydrocarbon Exposure and Glomerulonephrosis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Cases</th>
<th>Diagnosis*</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperace et al.</td>
<td>2</td>
<td>Goodpasture’s</td>
<td>Gasoline</td>
</tr>
<tr>
<td>Heale et al.</td>
<td>1</td>
<td>Goodpasture’s</td>
<td>Gasoline</td>
</tr>
<tr>
<td>Klavis and Drommer</td>
<td>1</td>
<td>Goodpasture’s</td>
<td>Gasoline-based paint spray</td>
</tr>
<tr>
<td>Beirne and Brennan</td>
<td>5</td>
<td>Goodpasture’s</td>
<td>Degreasing and paint</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>RPGN</td>
<td>Solvents and jet fuel</td>
</tr>
<tr>
<td>D’Apice et al.</td>
<td>2</td>
<td>Goodpasture’s</td>
<td>Gasoline mineral turpentine</td>
</tr>
<tr>
<td>Kleinke et al.</td>
<td>2</td>
<td>Anti-GBM nephritis</td>
<td>Organic solvent vapors</td>
</tr>
<tr>
<td>Daniell et al.</td>
<td>1</td>
<td>Subacute GN</td>
<td>Stoddard solvent</td>
</tr>
<tr>
<td>Von Scheele et al.</td>
<td>1</td>
<td>Epimembranous GN</td>
<td>Paint solvent</td>
</tr>
<tr>
<td>Ehrenreich et al.</td>
<td>4</td>
<td>Epimembranous GN</td>
<td>Solvents</td>
</tr>
<tr>
<td>Cagnolì</td>
<td>1</td>
<td>Epimembranous GN</td>
<td>?</td>
</tr>
</tbody>
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*GBM = glomerular basement membrane; RPGN = rapidly progressive glomerulonephritis; GN = glomerulonephritis.
plant. The three groups studied were comparable in age, duration of employment, duration of hydrocarbon exposure, and other factors. The authors concluded that long-term paint and solvent exposures are associated with renal impairment, micro-proteinuria without elevation of serum creatinine, and increased urinary protein excretion. These data indicate that chronic solvent exposure may be associated with early subclinical renal damage that may be adding to a chronic glomerulonephritis.

In a case–referent study, Porro, et al. 44 compared 60 patients whose chronic glomerulonephritis had been established by biopsy with 120 control subjects. Exposure assessment was based on scores from questionnaires. Both total and occupational solvent exposures were significantly higher in the cases than in the reference control group. The odds ratio of chronic glomerulonephritis for patients occupationally exposed to solvents was 3.9, and a logistic regression model showed a dose–response relationship of occupational exposures to solvents and glomerulonephritis. Histologic studies of the 60 patients with chronic glomerulonephritis ruled out other systemic disease and demonstrated the entire spectrum of glomerular diseases, the most common being IgA nephropathy. The subgroup of patients with IgA nephropathy appeared to have been significantly more exposed to solvents than the patients who had other non-glomerular diseases such as kidney stones. These data are in agreement with the hypothesis that the onset of glomerulonephritis could be related to chronic exposure to solvents of light intensity.

In a case–control study of a group of patients with diabetic nephropathy, De Broe et al. 45 demonstrated increased solvent exposure in 39% of the patients. These findings are in agreement with those of Yaqoob et al. 43 and indicate a particular sensitivity of patients with diabetic kidneys to the damaging effects of solvents. These findings are also in agreement with those of Goyer, 47 who reported that existing renal diseases, particularly hypertensive and diabetic nephropathies, predisposed to abnormal accumulation and excess blood levels of any nephrotoxic drugs and chemicals, as well as solvents. From a toxicologic and nephrologic point of view, it makes sense that individuals with underlying kidney disease are at a significantly increased risk for developing chronic glomerulonephritis as a result of solvent exposures.

**EPIDEMIOLOGIC ASSESSMENT**

Fewer than 10% of end-stage renal disease cases are characterized etiologically. 48 Clinically, many cases are classified histologically such as glomerulonephritis, but little effort is made to look for toxic factors. Indeed, the majority of the clinicians seeing patients with end-stage renal disease are not trained to look into occupational, environmental, or toxicologic issues that may be associated with it. Many cases of hypertensive end-stage renal disease that are presumed to be “idiopathic” may well result from industrial and/or environmental factors, among them, solvent exposures. Many of the problems hindering epidemiologic analysis stem from the reserve capacity of the kidney, which can function relatively adequately despite slowly progressive damage. End-stage renal disease typically is not diagnosed until considerable kidney damage has already occurred. Furthermore, kidney biopsies and postmortem examinations almost always show small kidneys, inadequate for histologic assessment, and therefore the cause is missed or misclassified as idiopathic or unknown.

Stengel et al. 49 looked at organic solvent exposure in relation to the risk of IgA nephropathy, and reported that the risk was highest among the most exposed group. Yaqoob et al. 43 showed an increased risk factor of 15.5 for development of glomerulonephritis in patients exposed to aliphatic solvents and a risk factor of 5.3 in patients exposed to halogenated solvents. Steenland et al. 50 after evaluating the risks and causes of end-stage renal disease, concluded that regular exposure to industrial solvents played a significant role in the development of chronic end-stage renal disease.

**MECHANISM OF SOLVENT-INDUCED GLOMERULONEPHRITIS**

Immune-mediated mechanisms play a major role in the pathogenesis of glomerular disease, in general. In the vast majority of the cases, antigen–antibody reactions occur and immune complexes form in the kidney, mainly around the glomerular capillary wall and mesangium. Cellular antigens, endogenous such as DNA and tumor antigens as well as exogenous such as viral antigens hepatitis B and C, drugs, and bacteria have been shown to be causative factors in human
glomerular immune-mediated diseases. The pathologic processes most often found in association with solvent exposure and chronic glomerular nephritis have been IgA nephropathy, Goodpasture’s syndrome, and proliferative glomerulonephritis.

Unlike the acute renal failure caused by hydrocarbons, where the renal damage is secondary to the nephrotoxins and mainly causes damage of the proximal tubule, chronic glomerular renal failure appears to be immunologically mediated. Among others, genetic factors may be involved in the pathogenesis of solvent-induced nephropathy. It has been suggested that the propensity to develop this autoimmune disease depends on a combination of a genetic component and an environmental component.24 Ravnskov,51 in a review of the pathogenesis of solvent-associated glomerulonephritis, suggested that solvents are immunosuppressives, and this effect is evident in several locations in the immunologic cascade. It includes impairment of leukocyte mobility and phagocytosis suppression, as seen in the benzene effects in mice.52 This suppression of the normal immune response may play a role in the pathogenesis of immune-mediated glomerular lesions.

Another suggested mechanism involves alteration in membrane permeability. Goodpasture’s syndrome is mediated by antibodies reactive with the glomerular basement membrane and alveolar basement membranes. Antibodies in experimental models can usually bind to alveolar basement membranes in vitro by indirect immunofluorescence. Experimental studies suggest that solvents alter the permeability of pulmonary capillaries, thereby allowing antiglomerular basement membranes to bind to the alveolar basement membranes.53 This mechanism supported by the observation of differential sensitivity to exposures due to genetic factors, since DR3 and DR4 antigens are more frequent in patients with toxic nephritis than in the general population.54,55

Zimmerman, et al.36 found that six of eight patients with Goodpasture’s syndrome had experienced extensive occupational exposures to solvents for periods ranging from four months to ten years, suggesting that interactions between the inhaled hydrocarbons and the lung and kidney basement membranes could induce autoantibodies to these membranes. Goyer47 suggested an autoimmune mechanism responsible for glomerular lesions following chronic exposure to solvents. Based on these studies, it is proposed that chronic exposure of susceptible individuals to low levels of solvents may induce an initial cell injury sufficient to damage cell membranes and to provide the antigen triggering the immune response, accelerating a cascade of reactions ending with glomerulonephritis.

CONCLUSION

Despite the availability of evidence from clinical observations, case studies, and epidemiologic analyses, some investigators have not included these data in common textbooks, and the ability to detect kidney disease early in occupational settings has not been yet achieved. Ravnskov56 recently analyzed and explained the available data on solvents relative to causation of chronic kidney disease, based on the Bradford Hill criteria for causation.57 While it is true that Bradford Hill did not intend for these “aspects” to be criteria, or a checklist for causation, some of Hill’s aspects are helpful in evaluating causation. The most important aspects of Hill commonly relied on to establish causation (not all aspects need to be satisfied, but rather the weight of the current scientific evidence also needs to be taken into account58) are strength of association, biological plausibility, temporal relationship, biological gradients, and consistency. The solvent–kidney disease association is supported by:

1. **Strength of association**: The case studies and cohort studies summarized in Tables 1 and 2.
2. **Biological plausibility**: Experimental studies in animals demonstrating solvent exposure and glomerulonephritis.
3. **Temporal relationship**: The case reports and case–control studies show that exposures to solvents were the only exposures that was followed by glomerulonephritis.
4. **Biological gradient (dose–response)**: Dose–response relationships were shown in several of the cases and case studies described.
5. **Consistency**: Both the experimental animal studies and the case studies were reported by several investigators from different medical centers from different locations in the world.

Based on the data described in this paper and based on the most recent paper by Ravnskov,59 solvent exposures can cause chronic glomerulonephritis and, in patients who already have underlying, mild chronic renal disease, can aggravate and hasten the course of end-stage renal failure. Worker education and early detection of renal disease may prevent further deterioration to end-stage renal failure. Obtaining an occupational exposure history of any patient who has end-stage renal failure of “unknown etiology” is recommended.

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**References**


