

Dr. Jens-Uwe Voss  
Dr. Markus Roller  
Dr. Inge Mangelsdorf

# **Nephrotoxicity of Organic Solvents**

## **Evaluation of the Literature**

This publication is the final report of a project „Nephrotoxic effects of solvents - a literature survey“ – Project F 5159 – on behalf of the Federal Institute for Occupational Safety and Health.

The responsibility for the contents of this publication lies with the authors.

Authors: Dr. Jens-Uwe Voss  
Dr. Markus Roller  
Dr. Inge Mangelsdorf

Fraunhofer Institute  
Toxicology and Aerosol Research, Hannover

Publisher: Federal Institute for Occupational Safety and Health  
Friedrich-Henkel-Weg 1-25, D-44149 Dortmund, Germany  
Telephone: +49 231 - 90 71 - 0  
Telex: +49 231 - 90 71 - 454  
e-mail: dortmund@buaa.bund.de  
Internet: [www.buaa.de](http://www.buaa.de)

Berlin:  
Nöldnerstr. 40-42, D-10317 Berlin, Germany  
Telephone: +49 30 - 5 15 48 - 0  
Telex: +49 30 - 5 15 48 - 170  
e-mail: berlin@buaa.bund.de

Dresden:  
Proschhübelstr. 8, D-01099 Dresden, Germany  
Telephone: +49 351 - 80 62 - 0  
Telex: +49 351 - 80 62 - 210  
e-mail: dresden@buaa.bund.de

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## CONTENTS

|   |           |
|---|-----------|
| Abstract  | 9         |
| Kurzreferat   | 10        |
| Résumé  | 11        |
| <b>1 INTRODUCTION</b>   | <b>13</b> |
| <b>2 NON-NEOPLASTIC RENAL DISEASES</b>                                      | <b>16</b> |
| 2.1 Acute renal failure   | 16        |
| 2.2 Chronic renal failure   | 18        |
| 2.2.1 Development   | 18        |
| 2.2.2 Incidence in the general population                                   | 20        |
| 2.3 Glomerulonephritis  | 20        |
| 2.3.1 Characterization  | 21        |
| 2.3.2 Classification  | 22        |
| 2.3.3 Incidence in the general population                                   | 23        |
| <b>3 MECHANISMS OF SOLVENT NEPHROTOXICITY</b>                               | <b>25</b> |
| 3.1 Metabolic activation of solvents  | 25        |
| 3.1.1 Cytochrome P450-mediated bioactivation                                | 25        |
| 3.1.2 $\beta$ -lyase mediated bioactivation of halogenated hydrocarbons     | 26        |
| 3.2 $\alpha_2$ -globulin related nephropathy                                | 28        |
| 3.3 Pathogenesis of solvent-dependent glomerulonephritis                    | 29        |
| <b>4 BIOMARKERS OF RENAL ALTERATIONS</b>                                    | <b>32</b> |
| 4.1 General remarks   | 32        |
| 4.2 Selected parameters as biomarkers for solvent induced renal alterations | 43        |
| 4.2.1 Total protein   | 43        |
| 4.2.2 Albumin   | 43        |

|          |   |           |
|----------|---|-----------|
| 4.2.3    | Transferrin   | 46        |
| 4.2.4    | IgG   | 47        |
| 4.2.5    | $\beta_2$ -Microglobulin  | 47        |
| 4.2.6    | Retinol-binding protein   | 47        |
| 4.2.7    | N-acetyl- $\beta$ -D-glucosaminidase  | 48        |
| 4.2.8    | Alanine aminopeptidase, $\beta$ -galactosidase, and $\beta$ -glucuronidase, leucin aminopeptidase, alkaline phosphatase | 49        |
| 4.2.9    | Lysozyme  | 49        |
| 4.2.10   | Tamm-Horsfall protein   | 49        |
| 4.2.11   | E-selectin in serum   | 50        |
| 4.2.12   | Laminin and anti-laminin antibodies   | 50        |
| 4.2.13   | Anti-glomerular basement membrane antibodies  | 50        |
| <b>5</b> | <b>CASE REPORTS – RESULTS AND DISCUSSION</b>  | <b>51</b> |
| <b>6</b> | <b>EPIDEMIOLOGICAL STUDIES – RESULTS AND DISCUSSION</b>   | <b>62</b> |
| 6.1      | Cohort studies and other longitudinal studies   | 62        |
| 6.2      | Case-control studies  | 67        |
| 6.2.1    | Description of studies  | 67        |
| 6.2.2    | Analysis of factors influencing the results   | 68        |
| 6.2.2.1  | Case definition   | 68        |
| 6.2.2.2  | Exposure assessment   | 72        |
| 6.2.2.3  | Selection of control groups and recall bias   | 74        |
| 6.2.2.4  | Interviewer bias (exposure suspicion bias)  | 76        |
| 6.2.3    | Conclusions   | 78        |
| 6.3      | Cross-sectional studies   | 95        |
| 6.3.1    | Description of studies  | 95        |
| 6.3.2    | Results   | 105       |
| 6.3.2.1  | Total protein   | 105       |
| 6.3.2.2  | Albumin   | 108       |
| 6.3.2.3  | Transferrin   | 111       |
| 6.3.2.4  | IgG   | 111       |
| 6.3.2.5  | $\beta_2$ -Microglobulin  | 112       |

|          |   |            |
|----------|---|------------|
| 6.3.2.6  | Retinol-binding protein   | 116        |
| 6.3.2.7  | N-acetyl- $\beta$ -D-glucosaminidase  | 117        |
| 6.3.2.8  | Alanine aminopeptidase, $\beta$ -galactosidase, and $\beta$ -glucuronidase                          | 121        |
| 6.3.2.9  | Lysozyme  | 124        |
| 6.3.2.10 | Tamm-Horsfall protein   | 124        |
| 6.3.2.11 | E-selectin in serum   | 125        |
| 6.3.2.12 | Laminin and anti-laminin antibodies   | 125        |
| 6.3.2.13 | Anti-glomerular basement membrane antibodies  | 127        |
| 6.3.3    | Evaluation and discussion   | 128        |
| 6.3.3.1  | Statistical analysis  | 129        |
| 6.3.3.2  | Analysis of site of action  | 131        |
| 6.3.4    | Conclusion  | 133        |
| <b>7</b> | <b>OVERALL EVALUATION</b>   | <b>153</b> |
| 7.1      | Evidence for an association between solvent exposure and renal effects                              | 153        |
| 7.2      | Parameters for biological effect monitoring at solvent-exposed workplaces – general recommendations | 155        |
| 7.3      | Future research needs   | 156        |
| <b>8</b> | <b>REFERENCES</b>   | <b>157</b> |
| <b>9</b> | <b>ANNEX</b>  | <b>176</b> |
| 9.1      | Tables of values of biological effect monitoring parameters   | 176        |
| 9.2      | List of abbreviations   | 206        |

## LIST OF FIGURES

|                  |   |     |
|------------------|---|-----|
| <b>Fig. 1.1</b>  | Solvents marketed in Western Europe   | 14  |
| <b>Fig. 2.1</b>  | Schematic illustration of nephron architecture  | 17  |
| <b>Fig. 4.1</b>  | Flow chart of cascade of events following exposure to renal toxins  | 33  |
| <b>Fig. 6.1</b>  | Results from meta-analysis of case-control studies  | 77  |
| <b>Fig. 6.2</b>  | Comparison of total protein concentration in urine of solvent-exposed workers and of non-exposed controls – part I                            | 106 |
| <b>Fig. 6.3</b>  | Comparison of total protein concentration in urine of solvent-exposed workers and of non-exposed controls – part II                           | 107 |
| <b>Fig. 6.4</b>  | Comparison of albumin concentration in urine of solvent-exposed workers and of non-exposed controls – part I                                  | 108 |
| <b>Fig. 6.5</b>  | Comparison of albumin concentration in urine of solvent-exposed workers and of non-exposed controls – part II                                 | 109 |
| <b>Fig. 6.6</b>  | Comparison of albumin concentration in urine of solvent-exposed workers and of non-exposed controls – part III                                | 110 |
| <b>Fig. 6.7</b>  | Comparison of transferrin concentration in urine of solvent-exposed workers and of non-exposed controls                                       | 112 |
| <b>Fig. 6.8</b>  | Comparison of $\beta_2$ -microglobulin ( $\beta_2$ M) concentration in urine of solvent-exposed workers and of non-exposed controls – part I  | 114 |
| <b>Fig. 6.9</b>  | Comparison of $\beta_2$ -microglobulin ( $\beta_2$ M) concentration in urine of solvent-exposed workers and of non-exposed controls – part II | 115 |
| <b>Fig. 6.10</b> | Comparison of retinol-binding protein (RBP) concentration in urine of solvent-exposed workers and of non-exposed controls                     | 116 |
| <b>Fig. 6.11</b> | Comparison of N-acetyl- $\beta$ -D-glucosaminidase (NAG) activity in urine of solvent-exposed workers and of non-exposed controls – part I    | 117 |
| <b>Fig. 6.12</b> | Comparison of N-acetyl- $\beta$ -D-glucosaminidase (NAG) activity in urine of solvent-exposed workers and of non-exposed controls – part II   | 118 |
| <b>Fig. 6.13</b> | Urinary NAG-excretion in metal industry workers exposed to chlorinated organic solvents   | 119 |
| <b>Fig. 6.14</b> | Comparison of alanine aminopeptidase (AAP) activity in urine of solvent-exposed workers and of non-exposed controls                           | 121 |
| <b>Fig. 6.15</b> | Comparison of $\beta$ -galactosidase ( $\beta$ Gal) activity in urine of solvent-exposed workers and of non-exposed controls                  | 122 |

|                  |   |     |
|------------------|---|-----|
| <b>Fig. 6.16</b> | Comparison of $\beta$ -glucuronidase ( $\beta$ Glu) activity in urine of solvent-exposed workers and of non-exposed controls  | 123 |
| <b>Fig. 6.17</b> | Comparison of lysozyme concentration in urine of solvent-exposed workers and of non-exposed controls                          | 124 |
| <b>Fig. 6.18</b> | Anti-laminin antibodies and laminin in serum in groups of solvent-exposed workers and of non-exposed controls                 | 126 |
| <b>Fig. 6.19</b> | Anti-glomerular basement membrane antibodies (AGBM) in serum in groups of solvent-exposed workers and of non-exposed controls | 127 |

## LIST OF TABLES

|                 |  |     |
|-----------------|--|-----|
| <b>Tab. 2.1</b> | Stages of renal insufficiency  | 19  |
| <b>Tab. 2.2</b> | Differentiation between nephritic and nephrotic syndrome   | 23  |
| <b>Tab. 2.3</b> | Clinical characteristics and differentiation of various forms of primary glomerulonephritides  | 24  |
| <b>Tab. 4.1</b> | Markers for detection of renal functional alterations  | 35  |
| <b>Tab. 4.2</b> | Normal values for various biomarkers of renal function in humans   | 40  |
| <b>Tab. 4.3</b> | Types of toxic kidney damage and corresponding markers   | 42  |
| <b>Tab. 4.4</b> | Classification and cut-off limits of albuminuria   | 44  |
| <b>Tab. 4.5</b> | Estimates of urine albumin excretion in healthy subjects   | 46  |
| <b>Tab. 4.6</b> | Control values for albumin excretion in the general population   | 46  |
| <b>Tab. 5.1</b> | Acute tubular toxicity of solvents – examples of case reports  | 54  |
| <b>Tab. 5.2</b> | Glomerular damage and solvent exposure – case reports  | 56  |
| <b>Tab. 6.1</b> | Cohort mortality studies of solvent-exposed workers – summary of data for deaths from renal or genitourinary diseases.                                 | 65  |
| <b>Tab. 6.2</b> | Weighted mean odds ratios (OR) for hydrocarbon exposure for patient groups with different renal functional status                                      | 72  |
| <b>Tab. 6.3</b> | Exposure scoring system for solvent and hydrocarbon exposure   | 74  |
| <b>Tab. 6.4</b> | Diagnostic classification of glomerulonephritis in case groups of case-control studies   | 79  |
| <b>Tab. 6.5</b> | Nephrotoxicity of hydrocarbon solvents – case-control studies  | 81  |
| <b>Tab. 6.6</b> | Overview of observed alterations of biomarkers in studies on solvent-exposed workers   | 98  |
| <b>Tab. 6.7</b> | Explorative statistical analysis of the frequency of "high" values for variables of urinary excretion in cross-sectional studies with solvent exposure | 130 |
| <b>Tab. 6.8</b> | Solvent-exposed groups with individual values of albumin concentration in urine exceeding normal range   | 131 |
| <b>Tab. 6.9</b> | Nephrotoxicity of hydrocarbon solvents – cross-sectional studies   | 134 |
| <b>Tab. 9.1</b> | Concentration of albumin in urine of solvent-exposed workers   | 177 |



|                  |  |     |
|------------------|--|-----|
| <b>Tab. 9.2</b>  | Concentration of $\beta_2$ -microglobulin ( $\beta_2$ M) in urine of solvent-exposed workers | 183 |
| <b>Tab. 9.3</b>  | Concentration of retinol-binding protein (RBP) in urine of solvent-exposed workers           | 187 |
| <b>Tab. 9.4</b>  | N-acetyl- $\beta$ -D-glucosaminidase (NAG) activity in urine of solvent-exposed workers      | 191 |
| <b>Tab. 9.5</b>  | $\beta$ -galactosidase ( $\beta$ Gal) activity in urine of solvent-exposed workers           | 196 |
| <b>Tab. 9.6</b>  | Alanine aminopeptidase (AAP) activity in urine of solvent-exposed workers                    | 197 |
| <b>Tab. 9.7</b>  | Concentration of total protein (TP) in urine of solvent-exposed workers                      | 199 |
| <b>Tab. 9.8</b>  | $\beta$ -glucuronidase ( $\beta$ Glu) activity in urine of solvent-exposed workers           | 203 |
| <b>Tab. 9.9</b>  | Concentration of transferrin (TRF) in urine of solvent-exposed workers                       | 204 |
| <b>Tab. 9.10</b> | Concentration of lysozyme in urine of solvent-exposed workers                                | 205 |

# NEPHROTOXICITY OF ORGANIC SOLVENTS – EVALUATION OF THE LITERATURE

## Abstract

This report surveys and evaluates the present state of knowledge regarding associations between occupational solvent exposure and alterations of renal functions and non-neoplastic kidney diseases, such as acute tubular damage and glomerulonephritides giving rise to chronic renal failure or end-stage renal disease.

The kidney may be damaged by solvents by several mechanisms, e.g. by reactive metabolites generated by the cytochrome P450 monooxygenases or by  $\beta$ -lyase mediated pathways. A variety of different markers in urine diagnostics has been proposed for detecting kidney changes, the most important being total protein, albumin, transferrin,  $\beta_2$ -microglobulin, retinol binding protein and N-acetyl- $\beta$ -D-glucosaminidase.

After short-term high exposure to different solvents, a number of cases with acute tubular damage have been described. Evidence for a possible association between solvent exposure and chronic kidney diseases – mainly glomerulonephritides – comes from a number of case-control studies. These studies also provide some evidence that solvent exposure could be associated with a progression of an existing glomerulonephritis rather than with the development of this disease. At present, however, these diseases cannot be ascribed to an exposure against specific solvents or solvent mixtures. Cohort mortality studies failed to show any association probably due to the rare occurrence of the diseases studied.

A statistical evaluation of data from cross-sectional studies indicates that a raised albumin excretion is more frequently found in groups of workers exposed to various solvents (toluene, styrene, aliphatic/aromatic hydrocarbon mixtures, tetrachloroethene, mixtures of chlorinated hydrocarbons) than in controls. Therefore, determination of albumin excretion could be a useful parameter in monitoring of solvent-exposed workers. However, further investigations are necessary to confirm the observed findings.

**Key words:** Albumin, biomarkers of renal function, epidemiology, nephrotoxicity, renal failure, glomerulonephritis, hydrocarbons, occupation, organic solvents, toxic nephropathy, urine analysis

# NEPHROTOXISCHE WIRKUNG VON ORGANISCHEN LÖSUNGSMITTELN – LITERATURRECHERCHE

## Kurzreferat

Der vorliegende Bericht gibt eine Zusammenstellung und Bewertung des gegenwärtigen Erkenntnisstands über Zusammenhänge zwischen einer Lösungsmittelexposition am Arbeitsplatz und Veränderungen der Nierenfunktion sowie nicht-neoplastischen Nierenerkrankungen wie akute Tubulusschäden und Glomerulonephritiden, die zu chronischem Nierenversagen bis hin zu terminaler Niereninsuffizienz führen können.

Lösungsmittel können über verschiedene Mechanismen die Niere schädigen, unter anderem durch reaktive Metaboliten, die durch Cytochrom-P450-abhängige Monooxygenasen oder  $\beta$ -Lyasen gebildet werden. Um Veränderungen der Nierenfunktion festzustellen, ist eine Vielzahl unterschiedlicher Marker in der Harn Diagnostik vorgeschlagen worden, von denen Gesamtprotein, Albumin, Transferrin,  $\beta_2$ -Mikroglobulin, Retinol bindendes Protein und N-acetyl- $\beta$ -D-Glucosaminidase die wichtigsten sind.

Nach kurzzeitiger hoher Exposition gegenüber verschiedenen Lösungsmitteln sind zahlreiche Fälle einer akuter Tubulusschädigung beschrieben worden. Hinweise auf einen möglichen Zusammenhang zwischen Lösungsmittlexposition und chronischen Nierenschädigungen, vor allem Glomerulonephritiden, ergeben sich aus einer Anzahl von Fall-Kontroll-Studien. Diese Studien liefern außerdem einige Anzeichen dafür, dass eine Exposition gegenüber Lösemitteln eher mit der Progression einer vorhandenen Glomerulonephritis als mit deren Entstehung assoziiert sein könnte. Der derzeitige Kenntnisstand lässt es jedoch nicht zu, diese Erkrankungen einer Exposition gegenüber bestimmten Lösungsmitteln bzw. -gemischen zuzuschreiben. Kohorten-Mortalitätsstudien haben keinen Hinweis auf irgendeinen Zusammenhang erbringen können, vermutlich wegen der Seltenheit der betrachteten Erkrankungen.

Eine statistische Auswertung der Daten aus Querschnittstudien spricht dafür, dass in Kollektiven, die gegenüber unterschiedlichen Lösungsmitteln (Toluol, Styrol, Aliphaten-Aromaten-Gemische, Tetrachlorethen, Mischungen von Chlorkohlenwasserstoffen) exponiert sind, häufiger als in den Kontrollgruppen eine erhöhte Konzentration von Albumin im Urin zu finden ist. Die Bestimmung der Albuminkonzentration im Urin könnte daher ein sinnvoller Parameter beim Monitoring lösungsmittel-exponierter Beschäftigter darstellen. Die beobachteten Zusammenhänge bedürfen jedoch der Bestätigung durch weitere praktische Untersuchungen.

**Schlagwörter:** Albumin, Arbeitsplatz, Biomarker der Nierenfunktion, Epidemiologie, Nephrotoxizität, Nierenversagen, Glomerulonephritis, Harnanalyse, Kohlenwasserstoffe, organische Lösungsmittel, toxische Nephropathie

# L'EFFET NÉPHROTOXIQUE DE SOLVANTS ORGANIQUES – UNE RECHERCHE BIBLIOGRAPHIQUE

## Résumé

Le rapport suivant nous donne une vue d'ensemble et une évaluation de l'état actuel des recherches sur les rapports de cause à effet entre une exposition à des solvants au lieu de travail et les altérations de la fonction rénale ainsi que les maladies rénales non-néoplastiques, comme par exemple les tubulopathies aiguës ou les glomérulonéphrites, maladies pouvant mener à une défaillance rénale chronique et même à une insuffisance rénale terminale.

Les solvants organiques peuvent causer des lésions rénales par le biais de différents mécanismes comme les métabolites réactifs produits par des monooxygénases à cytochrome P-450 ou des bêta-lyases. Une grande variété de différents marqueurs a été proposée afin de pouvoir identifier les changements de la fonction rénale lors de l'analyse de l'urine. A noter ici surtout la protéine totale, l'albumine, la transferrine, la bêta-2-microglobuline, le retinol binding protein et la N-acétyl-bêta-D-glucosaminidase.

De nombreux cas de tubulopathie ont été décrits à la suite d'une exposition élevée de courte durée à divers solvants. Plusieurs études cas-témoins indiquent un rapport possible entre l'exposition à des solvants et les maladies rénales chroniques, en particulier les glomérulonéphrites. De plus, ces études livrent plusieurs indices qui laissent supposer qu'une telle exposition est responsable de la progression d'une glomérulonéphrite déjà existante et non à l'origine de la maladie. Pourtant, l'état actuel des recherches ne permet pas d'imputer ces maladies à une exposition à certains solvants ou mélanges de solvants. Des études à cohorte sur la mortalité n'ont mis en évidence aucun rapport possible, probablement en raison de la rareté des maladies étudiées.

Une évaluation statistique des données établies lors d'études transversales indique que les collectifs exposés à différents solvants tel le toluol, le styrène, les mélanges aliphatiques/aromatiques, le tétrachloroéthène et les mélanges d'hydrocarbures chlorés, présentent plus fréquemment une concentration élevée d'albumine dans les urines que les groupes témoins. C'est la raison pour laquelle la détermination de la concentration d'albumine dans les urines pourrait représenter un paramètre utile pour le monitoring de personnes exposées aux solvants professionnels. Il sera toutefois nécessaire de poursuivre les recherches pratiques afin de confirmer les observations faites.

**Mots clés:** Albumine, analyse d'urine, biomarqueurs de la fonction rénale, épidémiologie, glomérulonéphrite, hydrocarbures, insuffisance rénale, lieu de travail, néphropathie toxique, néphrotoxicité, solvants organiques



# 1 Introduction

Many substances from different chemical categories (e.g. heavy metals such as cadmium, drugs such as aminoglycosid antibiotics and analgesics, some solvents) are known or suspected to cause acute or chronic "toxic nephropathies" in humans. This term is used to describe all acute or chronic disorders or malfunctions of the structural integrity or the excretory, endocrine, and metabolic function of the kidney which are caused by exogenous chemical substances (BAHNER and HEIDLAND, 1998).

The particular susceptibility of the kidney against toxic injury is related to kidney specific physiological features (BAHNER and HEIDLAND, 1998; ENDOU, 1998; GUDER, 1987; DEKANT and VAMVAKAS, 1993; PRICE et al., 1996; PRICE, 2000):

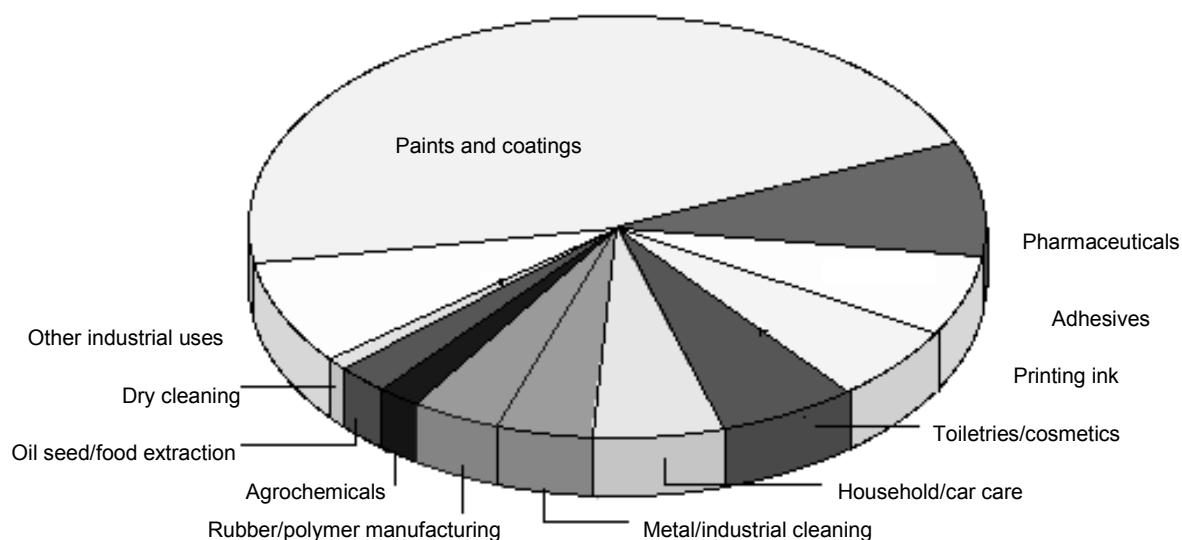
- A high renal blood flow: The kidneys make up only 0.5 % of the human body weight yet receive about 25 % of the heart minute volume. Within the kidney, the blood flows through the glomerular and the peritubular capillary system which are more intensely exposed to blood-borne chemicals than any other capillaries in the human body;
- effective transport systems, which may lead to an accumulation of chemicals in the renal tissues, especially in the tubular epithelium;
- intrarenal fluid retention by the counterflow principle (primary urine volume: about 150 - 180 l·d<sup>-1</sup>; final urine volume: 1 - 2 l·d<sup>-1</sup>): For substances with glomerular filtration or/and tubular secretion which are not or poorly resorbed in the tubules, their concentration in the tubular system compared to serum will increase several times;
- biotransformation of chemicals by xenobiotic-metabolizing enzymes, especially of the tubular epithelial cells, which may lead to the formation of toxic metabolites;
- a high oxygen and substrate demand of the renal cortex makes this region of the kidney vulnerable to substances impairing the cellular energy metabolism.

The relevance of certain diseases, e.g. diabetes and hypertension, in the etiology of chronic nephropathies is well known (BOEGE, 1998). In contrast, the role of nephrotoxins in the development or progression of renal failure is still not clear (ELSEVIERS and DE BROE, 1998). It is estimated that about 25 % of all cases of acute or chronic renal failure are attributed to nephrotoxic causes (BAHNER and HEIDLAND, 1998). Drugs (antibiotics, non-steroidal antiinflammatory drugs (NSAID) and analgesics, contrast media) probably play a greater role than industrial or household chemicals (solvents, heavy metals, pesticides) in acute renal failure (LAUWERYS and BERNARD, 1989) and probably also in chronic renal failure, but data are too limited to allow more accurate estimates. According to the European Dialysis and Transplant Association (EDTA-ERA), in about 4 % of all patients with primary renal disease requiring dialysis in Europe between 1980 and 1994, toxic injury – mostly due to use

of analgesics – was noted as the underlying cause of terminal renal failure. At the same time, for about 30 % of these patients, the etiology was unknown or missing. About 12 % of patients suffered from glomerulonephritis (MAISSONNEUVE et al., 2000). Glomerulonephritis has repeatedly been related to solvent exposure and the epidemiological studies will be discussed in this report.

It has been estimated that in the USA about four million workers are exposed to chemicals which, at least from data of animal experiments, are suspected to show nephrotoxic effects. Among these chemicals, solvents form a structurally heterogeneous group of chemicals with a wide-spread use for a variety of products and at different working places. Renal damage following acute inhalative exposure to solvents (turpentine) has been described in case reports more than a century ago (RHEINHARD, 1887; GLAESER, 1892).

Solvents are used for degreasing, dry-cleaning, and extraction of fats and oils, and can be found in a wide range of products including paints, thinners, glues, inks, and pesticides. The largest demand for solvents comes from the paint and coatings industry which uses almost two million tonnes every year in Western Europe (Fig. 1.1), but the demand in the pharmaceutical sector is steadily growing.



**Fig. 1.1** Solvents marketed in Western Europe (1995). Data from European Solvents Industry Group (ESIG), 1999.

Organic solvents are relatively stable volatile compounds, or mixtures of such compounds, which are liquid at temperatures between about 0 °C and 250 °C and are able to dissolve a wide range of organic compounds (AYRES and TAYLOR,

1989; HOTZ, 1994; SCHENKER and JACOBS, 1996). This definition includes groups of liquids that may be categorized according to their chemical composition in different, somewhat overlapping groups:

- "true" hydrocarbons: aliphatic, alicyclic, and aromatic hydrocarbon compounds, derived from petroleum distillation and refining;
- oxygenated compounds, e.g. alcohols, ketones, esters, ethers, glycols;
- halogenated compounds, e.g. chlorinated alkanes such as dichloromethane, and alkenes such as tetra- and trichloroethene;
- sulfur-containing compounds, e.g. carbon disulfide, dimethyl sulfoxide;
- nitrogen-containing compounds, e.g. dimethyl formamide.

Most organic solvents show a high volatility at room temperature, and therefore may easily evaporate. Uptake via inhalation therefore is an important route of exposure. Additionally, dermal contact may be frequent, especially if protection is not sufficient. As many solvents may penetrate the skin (AYRES and TAYLOR, 1989), dermal uptake of the liquid solvents may contribute considerably to the overall exposure to solvents. In contrast, dermal uptake of vapor is generally considered negligible, but may be important in case of some glycol ethers, e.g. 2-butoxyethanol (JOHANSON and BOMAN, 1991).

This report concentrates on occupational studies and possible consequences in occupational solvent exposure with respect to renal damage. A description and an evaluation of the vast amount of literature on experimental animal studies investigating effects of solvents is beyond the scope of this report. Data from animal experiments are only included as far as they concern some general mechanistic aspects of solvent nephropathy.

In this report, the renal diseases that have been associated with solvent exposure are characterized. This chapter is followed by a summarized overview on the hypotheses that have been offered as possible explanations how solvent exposure could be related to renal damage, especially to glomerulonephritis. The parameters that may be used as biomarkers for monitoring alterations of renal functions are described. Then, the available studies on humans will be presented, discussed, and evaluated. Finally, an overall evaluation of the evidence of an association between solvent exposure and nephropathy or alterations of functional parameters, respectively, will be given. Possible approaches for future occupational research and possible consequences with respect to the monitoring of workers at solvent-exposed workplaces will be discussed.



## 2 Non-neoplastic renal diseases

Non-neoplastic renal diseases may be classified into four, not entirely distinct categories (WEDEEN, 1992): According to their temporal course, renal diseases may be acute or chronic, and according to their primary site of injury, diseases may be glomerular or non-glomerular (tubular or/and tubulointerstitial).

In the following, a brief characterization is given of those renal diseases which have been described in case reports and investigated in epidemiological studies with respect to possible associations with solvent exposure.

### 2.1 Acute renal failure

A number of pharmaceuticals, e.g. antibiotics and analgesics, and chemicals such as various heavy metals and solvents have been described as causing acute renal failure (ARF) (PRICE, 1982). Data are too limited to allow a precise assessment of the frequency of chemical-induced acute renal disease. However, estimates of ARF amount to an annual incidence of about 20 p.m.p. (patients per million population), from which about 20 % may be due to drugs and chemicals (LAUWERYS and BERNARD, 1989).

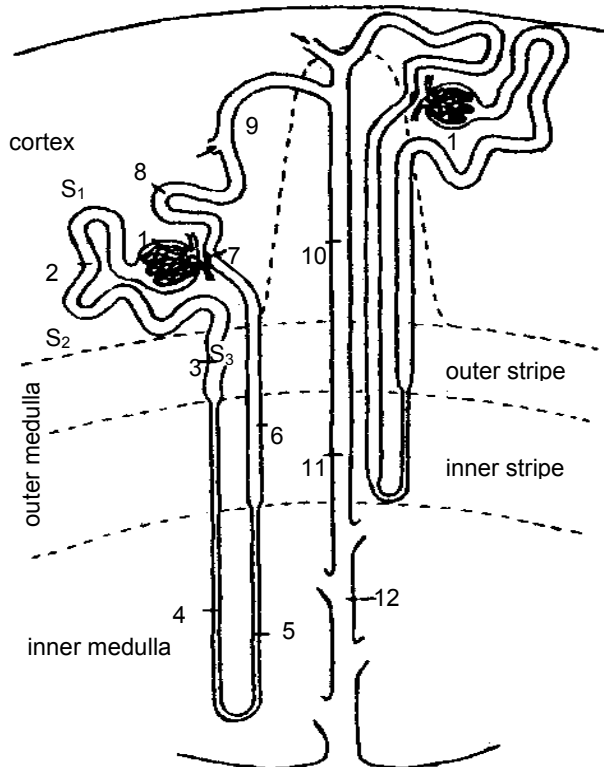
ARF develops within a short period of a few days or weeks. The most common types of ARF are acute tubular necrosis and tubulointerstitial nephritis, while acute glomerulonephritis, prerenal azotemia, or outlet obstruction are rarely seen (BAHNER and HEIDLAND, 1998; TESCHNER and HEIDLAND, 1998a; DEKANT and VAMVAKAS, 1993; WEDEEN, 1992).

Acute tubular necrosis accounts for an estimated 60 % of all cases of toxic ARF (DEKANT and VAMVAKAS, 1993). Typically, it is characterized by tubular dysfunction with glucosuria, proteinuria, and enzymuria (see Tab. 4.3, S. 42), and, in more severe cases, by a sudden reduction in urine production (oliguria < 300 ml urine/d or anuria) which lasts for several hours up to 14 days. During the oliguric phase, creatinine and urea concentration in serum increase due to the reduced glomerular filtration rate (GFR). Additionally, metabolic acidosis and hyperpotassemia (hyperkalemia) develop. Oliguria is followed by a marked increase in urine output (diuresis 3 – 10 l/d) during recovery.

Histopathologically, renal changes are confined to the tubules, the glomeruli are intact. The tubular epithelium undergoes changes ranging from swelling, ballooning, and hydropic changes to necrosis. The tubular lumen may contain desquamated cells, pigmented casts, or amorphous eosinophilic granular material. Both the proximal and the distal tubules and the collecting tubules may be affected (EHRENREICH, 1977).

Although untreated toxic ARF may be and formerly often was life-threatening or fatal, the prognosis today is usually good and recovery will mostly be obtained if adequate medical treatment including dialysis, if necessary, is given (LAUWERYS et al., 1985; GUDER, 1987; TESCHNER and HEIDLAND, 1998a).

There is no evidence by immunofluorescence studies to indicate the involvement of an immune-mediated mechanism in the development of solvent-related acute renal failure. It is more probable that the acute renal failure is the result of the direct injury of the toxic compound or its metabolites on the renal tubules (ROY et al., 1991). It is generally assumed that the occurrence of tubular lesions leads to a reduction of renal cortical perfusion. This reaction may be exacerbated by a passive backflow of glomerular filtrate across the damaged tubular lumen which, in combination with the lumen obstruction by cell debris, may account for the observed oligo- or anuria (PHILLIPS et al., 1988).



**Fig. 2.1** Schematic illustration of nephron architecture. A short- and a long-looped nephron with the collecting system are shown. 1: renal corpuscle including Bowman's capsule and glomerulus; 2: proximal convoluted tubule; 3: proximal straight tubule; 4: descending thin limb; 5: ascending thin limb; 6: distal straight tubule; 7: macula densa; 8: distal convoluted tubule; 9: connecting tubule; 10/11: cortical/outer medullary collecting duct; 12: inner medullary duct; S<sub>1</sub>, S<sub>2</sub>, S<sub>3</sub>: functionally different parts of proximal tubulus. Figure adapted from COMMANDEUR and VERMEULEN (1990).

While the renal changes are generally non-specific, some solvents have been associated with certain characteristic features, e.g. fatty vacuolization in tetrachloromethane or calcium oxalate deposition in ethylene glycol poisoning (EHRENREICH, 1977). The S<sub>3</sub> segment (Fig. 2.1) appears to be the site of nephrotoxic injury to some haloalkanes. Whether this is also true for the non-haloalkanes remains to be determined. This segment of the nephron is rich in the inducible type of mixed-function oxidases found on the endoplasmic reticulum, which during the process of

metabolism results in the formation of reactive metabolites, many of which are free radicals (KLUWE, 1981; ROY et al., 1991).

Besides a direct toxic effect on the tubulus, acute tubular necrosis may also develop secondary from excessive circulating heme pigments which are induced by rhabdomyolysis or hemolysis from toxins that break down muscle or red blood cells (WEDEEN, 1992).

Tubulointerstitial nephritis is another cause of acute renal failure accounting for about 15 % of all lesions in acute renal failure (NEILSON et al., 1989) or 40 % of all cases of toxic acute renal failure (DEKANT and VAMVAKAS, 1993). Acute tubulointerstitial nephritis is a hypersensitivity reaction which is known to occur following administration of certain drugs (e.g., antibiotics, diuretics, non-steroidal), but also high doses of lead. Histologically, infiltrates of monocytes in the cortical interstitium, interstitial oedema, and some tubular necrosis are observed, whereas tubular deposition of immune complexes is rarely seen. Analysis of urine reveals white blood cell casts, increased sodium excretion, and mild to moderate, mostly non-nephrotic proteinuria. Without renal biopsy, differentiation between acute tubular necrosis, subtle glomerulonephritis, or acute tubulointerstitial nephritis may be difficult (DEKANT and VAMVAKAS, 1993; NEILSON et al., 1989).

## **2.2 Chronic renal failure**

### **2.2.1 Development**

Unlike acute renal failure, chronic renal failure (CRF) develops slowly, but may be irreversible and mostly progressive. It results from any disease that causes gradual destruction of the kidneys and may range from mild dysfunction to severe, potentially life-threatening kidney failure. The most common renal causes of CRF are glomerulonephritis and tubulointerstitial nephritis (LAUWERYS and BERNARD, 1989; NEILSON et al., 1989; NUYTS et al., 1989; THOMAS, 1998b).

Chronic renal failure develops over the course of many years, as the internal structures of the kidney are slowly destroyed. Morphologically, progressive destruction involves two major processes: Firstly, accumulation of mesangial matrix and proliferation of mesangial cells leads to an obliteration of glomerular capillaries. Secondly, the extraglomerular interstitium is also involved, and a correlation between the extent of renal dysfunction and the magnitude of tubulointerstitial damage has been described (JACOBSON, 1991).

In the early stage, there are generally no clinical symptoms, and progression may be so gradual that symptoms do not occur until the functional capacity of the kidney is reduced to about one-tenth of normal. When a declining glomerular filtration rate (GFR) is used as a measure of renal function and serum creatinine concentration as an indicator of GFR, a transitional stage lasting for years can be observed in many patients (Tab. 2.1). During this stage, serum creatinine concentration slowly rises. Progression may continue to advanced renal failure (preterminal insufficiency) and,

finally, to terminal renal failure and end-stage renal disease (ESRD) with dialysis or transplantation (THOMAS, 1998b; WALSER, 1990).

Since CRF develops progressively and not step-wise, there is no clear-cut threshold for functional parameters to define the onset of CRF. E.g., NUYTS et al. (1995) characterized patients as suffering from CRF when the calculated creatinine clearance consistently dropped under the third percentile of the normal distribution in the general population. STENGEL et al. (1995, 1996) diagnosed CRF if the blood creatinine exceeded 150  $\mu\text{M}$  (17 mg/l), while JUNGERS et al. (1996) used a serum creatinine concentration  $\geq 200 \mu\text{M}$  ( $\geq 22.6$  mg/l) to differentiate between normal renal function and CRF, and according to SCHENA et al. (1997), chronic renal insufficiency was indicated by serum creatinine levels persistently above 15 mg/l (133  $\mu\text{M}$ ).

**Tab. 2.1** Stages of renal insufficiency (modified from ROCHE, 1999)

| Stage |   | Findings in serum   | Symptoms   |
|-------|---|---|--|
| I     | Limited renal capacity                              | SCr $\leq 12$ mg/l (106 $\mu\text{M}$ )                           | Decreased concentration ability  |
| II    | Moderate renal failure<br>(compensated retention)   | SCr 13 – 60 mg/l (115 – 530 $\mu\text{M}$ )<br>SU 0.5 – 1.5 g/l   | No or moderate clinical symptoms of renal insufficiency  |
| III   | Advanced renal failure<br>(decompensated retention) | SCr 60 – 120 mg/l (530 – 1060 $\mu\text{M}$ )<br>SU 1.5 – 2.5 g/l | Marked signs of renal insufficiency;<br>may be dealt with conservative measures                              |
| IV    | Terminal renal failure                              | SCr $> 120$ mg/l ( $\geq 1060 \mu\text{M}$ )<br>SU $> 2.5$ g/l    | Terminal loss of excretory (and endocrine) function, uraemia;<br>dialysis or renal transplantation mandatory |

0                      50                      100  
% renal function (GFR)

SCr: serum creatinine

SU: serum urea

End-stage renal disease (ESRD) occurs when chronic renal failure has progressed to terminal renal failure at which the kidneys are permanently functioning at less than 10% of their capacity. At this point, dialysis or kidney transplantation is of vital importance since the kidney function is so low that otherwise complications are multiple and severe, and death will occur from accumulation of fluids and waste products in the body.

Strictly speaking, ESRD is defined not only by the presence of irreversible renal failure that requires dialysis or transplantation, but also by the institution of such therapy, since patients dying of chronic uremia are not recorded as having ESRD in the existing kidney registries (PORT, 1993).

### 2.2.2 Incidence in the general population

While the annual incidence of acute renal failure is approximately 20 p.m.p., chronic renal diseases are probably about ten to 20 times more frequent (LAUWERYS and BERNARD, 1989). Recently, in a French study the annual incidence of CRF in adults was estimated to be about 260 p.m.p.. There was a steep increase with age, and the incidence was twice as high in males than in females. About 30 % of the patients had advanced renal failure with a serum creatinine concentration  $\geq 500 \mu\text{M}$  (56 mg/l) (JUNGERS et al., 1996).

The incidence of ESRD has been increasing in developed countries for many years. Bearing in mind the definition of ESRD (see above), this increase may not necessarily indicate an increased incidence of chronic renal failure but an increase in therapy. However, according to PORT (1993), two other factors are likely contributors: Firstly, competing risks such as death because of hypertensive or atherosclerotic coronary heart disease have been decreasing over the years (e.g. because of bypass surgery) so that in such cases the associated renal disease may become increasingly evident. Secondly, however, the possibility of an actual ("real") increase in renal disease must be considered.

In Germany, the annual incidence of adult patients (> 18 years of age) with ESRD (all causes) in 1996 was 156 p.m.p.. At the same year, the prevalence was 713 p.m.p., corresponding to a total number of 57803 patients who received dialysis or kidney transplant (FREI et al., 1999). A lower annual incidence of 60.1 p.m.p. and a prevalence of 405.4 p.m.p. have been reported for Denmark (BERTHOUX et al., 1996), and an annual incidence of at least 81 p.m.p. has been estimated in a study on a French suburban population (JUNGERS et al., 1996).

### 2.3 Glomerulonephritis

The most common cause of CRF are glomerulonephritides, followed by interstitial nephritis. According to THOMAS (1998b), 31 % of CRF are caused by glomerulonephritides and 21 % by interstitial nephritis. TESCHNER and HEIDLAND (1998b) report that the percentage due to GN is higher (about 40 %), and LAUWERYS and Bernhard (1989) even estimate that about 60 % of chronic nephropathies are primary glomerulonephritides.

With respect to an association with solvent exposure, glomerulonephritis (GN) is the pathological renal lesion which nearly exclusively has been investigated in epidemiological (mostly case-control) studies. Therefore, in the following some basic information on this type of lesion will be presented. In case of interstitial nephritis, there are practically no epidemiological data, but at best some few case studies reporting an association to solvent exposure, so this lesion will not be described any further in this report.

### 2.3.1 Characterization

The term "glomerulonephritis" (GN) is applied to a group of diseases which are characterized by inflammatory reactions of the glomerular capillaries with cell proliferation, more or less pronounced deposition of immune complexes at the basal membrane, and often gradual destruction of the glomeruli with progressive loss of kidney function.

Clinically, the most typical laboratory characteristic of most GN is a nephritic syndrome (Tab. 2.1), i.e. glomerular haematuria with increased occurrence of dysmorphic glomerular erythrocytes and reduced glomerular filtration rate (BALDAMUS and POLLOK, 1998; BLUMBERG et al., 1987; GUDER, 1987; THOMAS, 1998d). Initially, a selective glomerular proteinuria (esp. albuminuria) may be found, but due to alterations of the specificity of the glomerular filter and secondary tubular damage, a non-selective proteinuria may develop (GUDER, 1987). A nephrotic syndrome with proteinuria exceeding 3,5 g/d (mostly albumin), hypoalbuminemia, hyperlipoproteinemia, oedema, and hypertension may also develop, especially in case of membranous GN, the most common cause of nephrotic syndrome in adults (BALDAMUS and POLLOK, 1998; CAGNOLI et al., 1980; GUDER, 1987; COUSER, 1999; HEAF et al., 1999).

The disorders generally progress at widely variable rates, and some forms of GN may show spontaneous remission. If nephrotic syndrome (Tab. 2.1) is present and can be controlled, other symptoms may be controlled as well. However, in case of nephrotic syndrome that is resistant to medical treatment, end-stage renal disease is likely to develop.

The characteristics of some important forms of GN are summarized in Tab. 2.1. The most common form of GN in developed countries today is IgA nephropathy (COUSER, 1999; IBELS and GYÖRY, 1994). IgA nephropathy (Berger's disease) results from the deposition of immunoglobulin A (IgA) in the glomeruli, where it creates inflammation. The disease was not recognized as a cause of glomerular damage until the late 1960s, when immunofluorescence techniques were applied to renal biopsies that could identify IgA deposits in kidney tissue. Although initially regarded as a benign nephropathy, ESRD will occur in 10 – 15 % of all IgA nephropathy patients within a period of 15 years (WAKAI et al., 1999), and worldwide, IgA nephropathy is now recognized as a leading cause of ESRD in patients presenting for renal replacement therapy (IBELS and GYÖRY, 1994).

A rare form of a rapid-progressive GN is seen in case of a Goodpasture's syndrome. In its classical form, this is a disease affecting kidney and lung, though sometimes milder forms with minimal renal or no pulmonary involvement occur. In blood, specific antibodies against basal membrane antigen structures of the lung alveoles and the renal glomerulus (anti-GBM) are detectable. Histologically, a linear deposition of immune complexes along the basal membrane is present in the glomerulus (BOMBASSEI and KAPLAN, 1992; KELLER and NEKARDA, 1985; LAUWERYS et al., 1985; SEYMOUR, 1985; WHITWORTH et al., 1974).

### 2.3.2 Classification

The classification of GN may be performed according to various aspects (SEYMOUR, 1985; THEWS et al., 1991) such as

- etiology: postinfectious or non-postinfectious,
- pathogenesis:
  - deposition of circulating antigen-antibody complexes at the glomeruli or
  - reaction of specific antibodies with the glomerular basal membrane,
- histopathology: focal, diffuse or segmental,
- clinical presentation: nephritic with or without nephrotic syndrome,
- temporal course: acute or chronic,
- clinical association: primary and non-systemic, or secondary, associated with systemic disease.

In most patients, a diagnostic renal biopsy is performed for diagnosis and to histologically differentiate between a number of different forms of GN with different prognostic outcome. A classification scheme according to histopathological criteria was proposed by a commission under the auspices of the WHO in 1982. This scheme which is based on light microscopy findings, supplemented by immunofluorescence and, in specific cases, electron microscopy, has been widely used with some modifications by individual authors and was found to be of good reproducibility (Marcussen et al., 1995). Since a more detailed description of the morphological and clinicopathological classification of GN is beyond the scope of this report, the reader is referred to several overviews (SEYMOUR, 1985; BALDAMUS and POLLOK, 1998; COUSER, 1999; MAISSONNEUVE et al., 2000).

**Tab. 2.1** Differentiation between nephritic and nephrotic syndrome (Baldamus and Pollock, 1994)

|                       | <b>Nephritic syndrome</b> | <b>Nephrotic syndrome</b> |
|-----------------------|---------------------------|---------------------------|
| Course                | Acute                     | Chronic                   |
| Oedema                | +                         | ++ to +++                 |
| Hypertonia            | + to +++                  | (+) to +                  |
| Creatinine clearance  | ↓ to ↓↓↓                  | no to ↓                   |
| Hematuria             | + to +++                  | (+)                       |
| Proteinuria           | < 3 g/d                   | >> 3 g/d                  |
| Hypo-/dysproteinaemia | (+)                       | + to +++                  |
| Hyperlipidaemia       | no                        | ++                        |

(+), +, ++, +++: slight, some, moderate, pronounced

↓, ↓↓, ↓↓↓: some, moderate, pronounced decrease

### 2.3.3 Incidence in the general population

Overall, glomerulonephritis is a rare disease. In a recent study in Denmark, an annual incidence of biopsy-proven cases of 39 p.m.p. and an overall incidence (including non-biopsied cases) of 73 p.m.p. have been reported (HEAF et al., 1999).

In developed countries, the most common form of glomerulonephritis which is seen clinically today is IgA-nephropathy. Incidences of biopsy-proven cases of IgA nephropathy ranged from 1.8 patients p.m.p. in Denmark (1985 – 1987; HEAF et al., 1999) to 8.4 in Italy (1993, SCHENA et al., 1997). However, as IgA nephropathy may often remain clinically silent for many years, it may go undetected. Thus, the total number of cases with IgA-nephropathy will certainly be considerably higher, but it is difficult to determine how many people are in the early stages of IgA nephropathy, when specific medical tests would be the only way of detection. IgA nephropathy appears to affect men more than women. Although IgA nephropathy is found in all age groups, young people rarely display signs of kidney failure because the disease usually takes several years to progress to the stage where it causes detectable complications.



**Tab. 2.1** Clinical characteristics and differentiation of various forms of primary glomerulonephritides (GN) (BALDAMUS and POLLOK, 1998; COUSER, 1999; SEYMOUR, 1985; IBELS and GYÖRNY, 1994)

| Type                            | Acute endocapillary  | Goodpasture syndrome <sup>a</sup>                      | Membranous  | Membranoproliferative (mesangio-capillary)                | (Mesangio-proliferative) IgA-nephropathy           |
|---------------------------------|--|--|---|---|--|
| Etiologic factors               | Idiopathic or postinfectious (esp. Poststreptococcal) inflammation     | Unknown  | Secondary to other diseases or medical treatment        | Primary cause unknown (secondary to systemic diseases)    | Postinfectious?                                    |
| Incidence (p.m.p.) <sup>d</sup> | 0.7 <sup>c</sup> ; 1.7 <sup>b</sup>                                    | 0.1 <sup>c</sup>                                       | 4.8 <sup>b</sup>  | 2.1 <sup>b</sup>  | 8.4 <sup>c</sup>                                   |
| Histology, cell proliferation   | Endothelium, mesangium   | Endothelium, mesangium, epithelium of Bowman's capsule | Not marked  | Mesangium   | Mesangium  |
| Immune complex deposition       | Mainly at outer side of basal membrane                                 | Along capillaries and in mesangium, linear             | Outside of basal membrane, subepithelial                | Subendothelial, thickening and doubling of basal membrane | IgA complex in mesangium                           |
| Urine diagnostic                | Haemat-, erythrocyturia, non-selective proteinuria, GFR may be reduced | Hematuria, proteinuria                                 | Non-selective proteinuria                               | Erythrocyturia, proteinuria, reduced GFR                  | Microhaematuria, slight, non-selective proteinuria |
| Prognosis                       | Usually complete recovery  | ESRD, without treatment often fatal                    | 1/3 patients: recovery<br>1/3: no progress<br>1/3: ESRD | Prognedient, ESRD   | Mostly good, but may progress to ESRD              |

a: a rapid-progressive GN (RPGN) with circulating antibodies against basal membrane of lung alveoles and renal glomerulus (AGBM)

b: annual incidence of biopsy-proven cases in Denmark between 1985 – 1997 (HEAF et al., 1997)

c: annual incidence of biopsy-proven cases in Italy in 1993 (SCHENA et al., 1997)

d: p.m.p.: patients per million population

### **3 Mechanisms of solvent nephrotoxicity**

Solvents represent a broad group of substances with different chemical structures. Therefore, it cannot be expected that the mechanism of action will be similar for all solvents. Furthermore, at many workplaces a number of different solvents are used, and combination effects of nephrotoxicants may occur (JONKER et al., 1996). Nephrotoxic effects may be due to long term exposure to low concentrations or to repeated short-term peak exposure. Due to saturation of certain metabolic pathways a different mechanism may be responsible in the latter case.

#### **3.1 Metabolic activation of solvents**

Experimental animal studies have shown that a number of xenobiotics require enzymatic transformation to reactive metabolites to elicit their toxic effects in the kidney. This bioactivation may take place in the kidney or in extrarenal tissues, or extrarenally formed metabolites may be further metabolized to toxic products in the kidney. Different metabolic pathways are involved in these reactions.

The following brief overview is restricted to the most important pathways which may contribute to the metabolism-mediated renal toxicity of solvents and illustrated by selected examples.

Other activation pathways, especially via the prostaglandin synthase, are important for the metabolic activation of other kidney toxins, but a role in solvent nephrotoxicity has not yet been demonstrated. Oxidation via alcohol dehydrogenase is an important pathway for the metabolism of alcohols, but with respect to kidney damage it is relevant in the special case of acute toxicity of ethylene glycol only. These pathways have therefore not been included. For a more detailed insight into the role of renal biotransformation, several reviews are available (ANDERS and DEKANT, 1998; COMMANDEUR and VERMEULEN, 1990; DEKANT and HENSCHLER, 1999; DEKANT and VAMVAKAS, 1996; GOLDSTEIN et al., 1990; KLUWE et al., 1981; LOCK, 1988; NAGELKERKE and BOOGAARD, 1991).

##### **3.1.1 Cytochrome P450-mediated bioactivation**

Cytochrome P450 dependent monooxygenases are the most prominent enzymes involved in solvent metabolism. Whereas the role of hepatic cytochrome P450-mediated bioactivation of solvents in liver damage is well-studied, much less direct evidence has been presented for the involvement of the corresponding renal enzymes in kidney damage.

The activity of cytochrome P450 monooxygenases in the kidney usually is lower than in the liver. Moreover, the localization and the activity of the cytochrome P450 enzymes along the nephron is heterogenous. This may have important consequences with respect to the site of toxic action in case of solvents which require bioactivation. Spectrophotometric and immunohistochemical determinations could

detect cytochrome P450 only in the cortex and the outer stripe of the outer medulla, especially in the S<sub>2</sub> and S<sub>3</sub> segments (for a schematic view of nephron architecture, see (Fig. 2.1) (COMMANDEUR and VERMEULEN, 1990). The proximal tubules seem to contain the highest concentration (DEKANT and VAMVAKAS, 1996). However, enzyme activity has been demonstrated also in the inner stripe of the outer medulla and the inner medulla (COMMANDEUR and VERMEULEN, 1990).

Several isoenzymes of cytochrome P450 have been isolated and characterized from the renal cortex. The renal expression of an enzyme closely related to hepatic cytochrome P450 2E1 seems most relevant for the bioactivation of solvents. Immunohistochemically, sex- and species-specific differences in the activity of this enzyme have been detected, the activity in kidney of male mice being higher than of female mice and both sexes of rats (DEKANT and VAMVAKAS, 1996).

The nephrotoxicity of trichloromethane (chloroform) and of 1,1-dichloroethene (1,1-DCE) in laboratory animals represent two examples for this type of metabolic activation (COMMANDEUR and VERMEULEN, 1990; DEKANT and VAMVAKAS, 1996; GOLDSTEIN et al., 1990; KLUWE, 1981). Both compounds induce lesions to the proximal tubules in male mice, but less so in rats and not in female mice. Thus, the pattern of lesions coincides with the observed distribution and activity of the P450-dependent monooxygenases.

Another pathway that may lead to renal injury may involve hepatic cytochrome P450-mediated biotransformation of substances to metabolites which are toxic to the kidney. This has been suggested as an alternative or additional pathway in the renal toxicity of 1,1-DCE. One may speculate that the hepatic biotransformation of other non-halogenated solvents may also produce metabolites that are directly toxic to the kidney or may interfere with important renal functions. An example could be 2,2,4-trimethylpentane, a constituent of aliphatic hydrocarbon mixtures. Hepatic biotransformation leads to 2,4,4-trimethylpentan-2-ol, a metabolite involved in the development of the  $\alpha_{2u}$ -globulin-associated nephropathy in male rats. This type of nephropathy seems to be common and may be caused by other solvents in male rats as well, but probably is of little relevance for humans (see chapter 3.2).

### 3.1.2 $\beta$ -lyase mediated bioactivation of halogenated hydrocarbons

Several halogenated alkenes are nephrotoxic in rodents. The metabolism of such halogenated alkenes is an example for a complex interaction of both inactivation and activation reactions in which both liver and kidney are involved. The current knowledge of the so-called  $\beta$ -lyase mediated bioactivation has recently been reviewed by DEKANT and HENSCHLER (1999) and ANDERS and DEKANT (1998). Briefly, nephrotoxic chlorinated haloalkenes (e.g. HCB, hexachloro-1,3-butadiene) undergo glutathione-S-transferase-catalysed reactions with glutathione (GSH). In a first step, they are metabolized largely in the liver to give chloroalkenylglutathione S-conjugates. These conjugates are excreted in the bile and pass into the small intestine. In the bile and the intestinal cells, they are hydrolyzed to the corresponding cysteinylglycine- and cysteine S-conjugates. S-conjugates may either be excreted

with the feces, undergo enterohepatic circulation, or, after they passed the liver, enter the systemic circulation and are transported to the kidneys. Mercapturic acids that may have been formed in the liver also reach the kidney via the blood stream. In the kidney, S-conjugates may reach the target cells in the proximal tubulus via glomerular filtration and tubular reabsorption from the urine or by basolateral transport from the blood, or both. In the proximal tubular cells, due to the high activity of  $\gamma$ -glutamyltransferase, dipeptidase, and aminoacylase, GSH-S-conjugates, cysteinylglycine-S-conjugates, and mercapturic acids all can be broken down with the formation of the corresponding cysteine-S-conjugates. The cysteine-S-conjugates inside the proximal cells may be secreted into the blood thus undergoing renal-hepatic-circulation, be acetylated and excreted as mercapturic acids (which so are both degraded and synthesized in these cells) or they may be broken down by  $\beta$ -lyase-catalysed reactions. The latter results in the formation of highly reactive thio-ketenes which are presumed to be the ultimate metabolites damaging the proximal tubular cells and being responsible for the nephrotoxic (and carcinogenic) effects.

It has been shown that the enzymes of the  $\beta$ -lyase bioactivation pathway are also present in human tissues including those of the kidney (ANDERS and DEKANT, 1998). However, *in vitro* studies revealed that the  $\beta$ -lyase activity from human kidney to a number of haloalkenyl S-conjugates is severalfold lower than that from rat tissues (HAWKSWORTH et al., 1996; MCCARTHY et al., 1994).

The important industrial solvents tetra- and trichloroethene are also metabolized via the  $\beta$ -lyase pathway (ANDERS and DEKANT, 1998; COMMANDEUR and VERMEULEN, 1990; DEKANT and VAMVAKAS, 1996). However, in contrast to HCB, which seems to be metabolized exclusively via glutathione conjugation, tri- and tetrachloroethene are mainly metabolized by cytochrome P450; glutathione conjugation represents only a minor pathway (LOCK, 1988; DEKANT and VAMVAKAS, 1996).

The excretion of N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine (TCVC) in tetrachloroethene and of N-acetyl-S-(2,2-dichlorovinyl)-L-cysteine (DCVC) in trichloroethene exposed persons has provided evidence that these solvents are also metabolized via the  $\beta$ -lyase pathway in humans (BRÜNING et al., 1998). However, comparison of data from *in vitro* and *in vivo* metabolic studies suggest that the glutathione S-conjugate formation and  $\beta$ -lyase-dependent bioactivation of TCVC in tetrachloroethene metabolism is much higher in rats than in humans (DEKANT et al., 1998; PÄHLER et al., 1999; VÖLKEL et al., 1998). In case of trichloroethene, limited *in vitro* data also indicate that the rat renal  $\beta$ -lyase activity to generate DCVC may be higher than that in humans (HAWKSWORTH et al., 1996). However, *in vivo* studies suggest that bioactivation of trichloroethene in rats and humans is qualitatively and quantitatively comparable (VAMVAKAS et al., 2000; BERNAUER et al., 1996), but it must be kept in mind that the overall contribution of this pathway in the metabolism of trichloroethene is very low (LOCK, 1988).

In conclusion, the data for the widely used solvents tetrachloro- and trichloroethene suggest that the  $\beta$ -lyase mediated bioactivation of haloalkenes is active in humans. However, quantitative species-specific differences and the contribution of other

pathways seem to be important for the assessment of nephrotoxic risk of these solvents for humans.

### 3.2 $\alpha_{2u}$ -globulin related nephropathy

Exposure to a number of solvents leads to hyaline droplet formation in the kidney tubules of male rats. Well-known examples are mixtures of hydrocarbons such as unleaded gasoline, white spirits and related solvents, and limonene (SWENBERG and LEHMAN-MCKEEMAN, 1999). Structure-activity-relationship studies have been carried out with a variety of aliphatic and cycloaliphatic hydrocarbons (e.g., BOMHARD et al., 1990).

The nephrotoxic activity of these substances is characterized by the following changes:

- accumulation of hyaline droplets in the cells of the S2-segment of the proximal convoluted tubules;
- $\alpha_{2u}$ -globulin accumulation in hyaline droplets;
- dilatation and granular cast formations in the medullary tubules;
- degeneration and regeneration of cortical tubular epithelium.

Associated with these histological changes an increased excretion of albumin, RBP, and NAG in urine can be found (VERPLANKE et al., 1999).

Because this process is linked to the development of kidney tumors in male rats, it has been the objective of many studies with respect to its relevance for humans. The current understanding of the development of the  $\alpha_{2u}$ -globulin-associated nephropathy has been summarized by DIETRICH (1997) and DEKANT and VAMVAKAS (1996). Briefly, male and female rats, but not other rodents, dogs, or primates including humans, synthesize low molecular weight proteins called  $\alpha_{2u}$ -globulin in different organs, e.g. the lacrymary, salivary and perianal glands. However, the major urinary protein of male rats is a hepatic form of  $\alpha_{2u}$ -globulin which is exclusively synthesized by male, but not by female rats. The  $\alpha_{2u}$ -globulin forms synthesized in small amounts by female rats are also excreted via the urine, but show distinct differences to the male rat forms of  $\alpha_{2u}$ -globulin. The synthesis and high rate of excretion of the hepatic form of  $\alpha_{2u}$ -globulin, the affinity of some chemicals or their metabolites for binding to this protein, and the reduced enzymatic breakdown of the chemical- $\alpha_{2u}$ -globulin-complex in lysosomes of the proximal tubule epithelial cells are thought to lead to an accumulation of these complexes in the renal cortex of male rats that become apparent as hyaline droplets. However, these processes are not fully understood, and alternative explanations have been presented. According to MELNICK and KOHN (1999),  $\alpha_{2u}$ -globulin may serve to increase the concentration of the toxic agent in the male rat kidney. In any case, further typical lesions include single-cell necrosis, exfoliation of cells into the proximal lumen, granular cast formation, and tubular hyperplasia (RODGERS and BAETCKE, 1993). Due to the species- and sex-specific

synthesis of this low molecular weight protein, this type of nephropathy (and the subsequent development of kidney tumors) is found in exposed male rats but not in female rats. Male or female mice, rabbits, or guinea pigs which lack  $\alpha_{2u}$ -globulin also do not develop this type of nephropathy. Moreover, it does not occur in male NCI Black Reiter rats (also named NIH black rat), a strain which lacks measurable production of  $\alpha_{2u}$ -globulin (RIDDER et al., 1990; DIETRICH and SWENBERG, 1991).

In humans with renal disease, a male-specific low-molecular weight protein was identified in urine (BERNARD and LAUWERYS, 1991). This protein ("protein 1") shows some similarity to the  $\alpha_{2u}$ -globulin of male rats, but unlike this, it does not bind hydrocarbon metabolites such as 2,4,4-trimethylpentan-2-ol. Furthermore, its concentration is several orders of magnitude lower than that of  $\alpha_{2u}$ -globulin in urine of male rats (VAMVAKAS and DEKANT, 1996).

In reports of the US-EPA (US-EPA, 1991; RODGERS and BAETCKE, 1993), the data on the development of male specific rat nephropathy by certain solvents were summarized and evaluated with respect to the accumulation of  $\alpha_{2u}$ -globulin. It was considered that humans are not at risk of developing this special type of nephropathy since they seem to be unable to synthesize  $\alpha_{2u}$ -globulin and the secretion of proteins is in general less than that of the rat. Furthermore, the proteins are either not related structurally to  $\alpha_{2u}$ -globulin or do not bind compounds that bind to  $\alpha_{2u}$ -globulin (BORGHOFF et al., 1991; BAETCKE et al., 1991; GOLDSTEIN and SCHNELLMANN, 1996). Therefore, the  $\alpha_{2u}$ -globulin-mediated pathways that lead to solvent toxicity in male rats are unlikely to offer a mechanism for nephrotoxicity in humans.

### 3.3 Pathogenesis of solvent-dependent glomerulonephritis

From data on bioactivation (see chapter 3.1) as well as case reports in humans (see chapter 5), it seems that the renal tubuli are the main target of toxic effects of chemicals in the kidney. On the other hand, in case-control studies (see chapter 6.2) glomerulonephritides seem to be associated with solvent exposures. Several hypotheses have been developed that try to offer possible explanations for the generation of solvent-related glomerulonephritides. These hypothesis have been summarized in several publications (NELSON et al., 1990; HOTZ, 1994; ROY et al., 1991; YAQOUB et al., 1992; RAVNSKOV, 1998).

According to these hypotheses, two main ways of action are conceivable: the immunological and the toxicological. Both ways do not exclude each other, but could be active concurrently or sequentially (HOTZ, 1994).

One of the first hypotheses of an immunological mechanism suggests that solvents could damage the capillary basement membrane of the alveoles (ABM) in the lung and/or the glomeruli (GBM) in the kidney, inducing an antigen-antibody reaction that leads to glomerulonephritis. This idea is based on case reports that Goodpasture's syndrome (see Tab. 2.1 and chapter 5), a disease which involves the development of anti-ABM and anti-GBM antibodies, has been described following exposure to organic solvents (NELSON et al., 1990). Since the antigen is cryptic (concealed within the type IV collagen of the basal membrane), it has been proposed that tissue-

damaging agents which injure the basement membrane may expose the antigen, facilitating the binding of anti-GBM antibodies (BOMBASSEI and KAPLAN, 1992). In an experimental animal study, it was observed that when anti-GBM antibodies were injected into rabbits, these antibodies became bound to alveolar basement membrane after intratracheal gasoline instillation, but not after saline installation. While this supports the idea that prior damage to alveolar structures may be a prerequisite for anti-GBM antigen deposition in the alveoles, this study did not analyse de-novo synthesis of antibodies following hydrocarbon exposure (BOMBASSEI and KAPLAN, 1992). Moreover, lung damage following gasoline instillation is due to the specific physical properties of the liquid and bears no analogy to inhalation of hydrocarbon vapors.

Goodpasture's syndrome is a very rare disease (Tab. 2.1) which typically evolves rapidly, while most cases of glomerulonephritis which have been supposed to be related to solvent exposure in epidemiological studies are classified as other, more common types of chronic glomerulonephritides. Therefore, other mechanisms must play a role.

As another immunological mechanism, it has been hypothesized that glomerular damage may result from an indirect immunological process mediated by tubular antigenic material. In membranous nephropathy, renal tubular epithelial antigen, immunoglobulins, and complement have been found in glomerular capillaries (EHRENREICH, 1977). One may speculate that constant low grade tubular damage in susceptible individuals due to chronic solvent exposure may provoke local autoimmunity by releasing either sequestered or altered tubular antigens (YAQOOB et al., 1993a). Some support for this hypothesis comes from the observation that gold and mercury, two substances that may cause glomerulonephritis in humans, may also damage the renal tubuli (Cahen et al., 1989; DEKANT and VAMVAKAS, 1993). Furthermore, experimental studies of gold-induced nephropathy in rats have shown that gold was present in the tubular epithelium, where it may induce an immunogenic response, but was not found in the glomeruli where lesions were observed (EHRENREICH, 1977). However, experimental evidence of a similar action of solvents is lacking.

Toxic damage to the tubuli as the primary lesion is in the foreground of a further hypothesis. The idea is based on observations from experimental exposure of animals to hydrocarbons. These studies have sporadically produced glomerular lesions, but this has generally been accompanied by tubular or tubulointerstitial damage (MUTTI, 1996). Therefore, the primary event may be a toxic tubulointerstitial reaction, the deposition of glomerular immune complexes being secondary (RAVNSKOV, 1989, 1992, 1998). In this context, it has been suggested that repeated peak exposures might induce tubular damage (HOTZ, 1994).

The hypothesis of a primary toxic effect at the tubules seems to be supported by the observation that in chronic kidney diseases morphometric studies of the kidney tissue reveal a striking correlation between the extent of renal dysfunction and the magnitude of tubulointerstitial disease (NATH, 1992). The main morphological expression of several disease processes is in the tubulointerstitium and interstitial damage has a

central role in loss of renal function (FINE et al., 1993; JACOBSON, 1991). However, it remains to be proven whether tubulointerstitial abnormalities found in primary glomerular diseases are a secondary event due to ischaemic tubular injury from disruption of the peritubular blood supply following glomerular destruction, or whether there is a destructive process that attacks both the interstitium and the glomerulus (JACOBSON, 1991).

The aforementioned hypotheses are based on the assumption that solvents are a primary cause of glomerulonephritis. However, it has also been suggested that solvents may have a secondary effect on glomerular damage which has been initiated by other toxic substances, immune reactions or systemic diseases, for example diabetes or hypertension. In this case, solvent exposure could lead to a progression of different types of glomerulonephritides. As will be shown in chapter 6.2, solvent exposure has indeed been associated in case-control studies with several types of glomerulonephritis, and additionally, there is some evidence from these studies that solvent exposure is related to the progression of renal failure in glomerulonephritis. Preliminary data from a recently published animal study indicate that adriamycin-induced nephropathy is more severe in rats which are also exposed to styrene (MUTTI et al., 1999). However, the doses of adriamycin used to induce renal damage were very high (about acute LD<sub>50</sub>), and additional data are necessary to more explicitly draw out this hypothesis.

Individual susceptibility is generally assumed to play a role in glomerulonephritis, because this disease is rare, whereas exposure to organic solvents is very common. There is some evidence that several forms of glomerulonephritides, including Goodpasture's syndrome, membranous nephropathy, and IgA nephropathy, have human leukocyte antigen (HLA) associations (BOMBASSEI and KAPLAN, 1992; NELSON et al., 1990; IBELS and GYÖRY, 1994). Interindividual variations in xenobiotic-metabolizing enzymes may influence biotransformation of solvents and could play a role in individual susceptibility. In one study on a group of patients with primary glomerulonephritis and an elevated hydrocarbon exposure, an increased frequency of genes encoding for certain variants of glutathione transferases and N-acetyl transferases was found in a subgroup with membranous glomerulonephritis, but not for the whole group (PAI et al., 1997). Further studies are necessary before a relationship between solvent exposure, biotransformation, and individual susceptibility to develop certain types of glomerulonephritides may be hypothesized.

In conclusion, several mechanisms have been suggested how exposure to solvents could be related to the development of glomerulonephritis, all of which are largely hypothetical. This does not argue against a role of solvents, but indicates the necessity of additional data. It must be remembered that the causative agents in most forms of human glomerulonephritis are unknown, and that, besides some infectious agents, other stimuli must be involved in the development of this complex disease (COUSER, 1999).



## 4 Biomarkers of renal alterations

### 4.1 General remarks

Usual clinical parameters which are used to assess renal injury include serum creatinine concentration, blood urea nitrogen levels, and glomerular filtration rate (GFR). However, these tests are rather insensitive, since they show abnormal findings only when a major impairment of renal excretory function due to a large reduction in effective nephron capacity has already developed. This may be the case following acute exposure to high concentrations of solvents (by accident, in suicidal purpose, or by abuse in "sniffers"), when acute renal damage is showing up as rapidly developing organ failure. However, such heavy effects are likely to occur only at exposure levels which are rarely found at the workplace today.

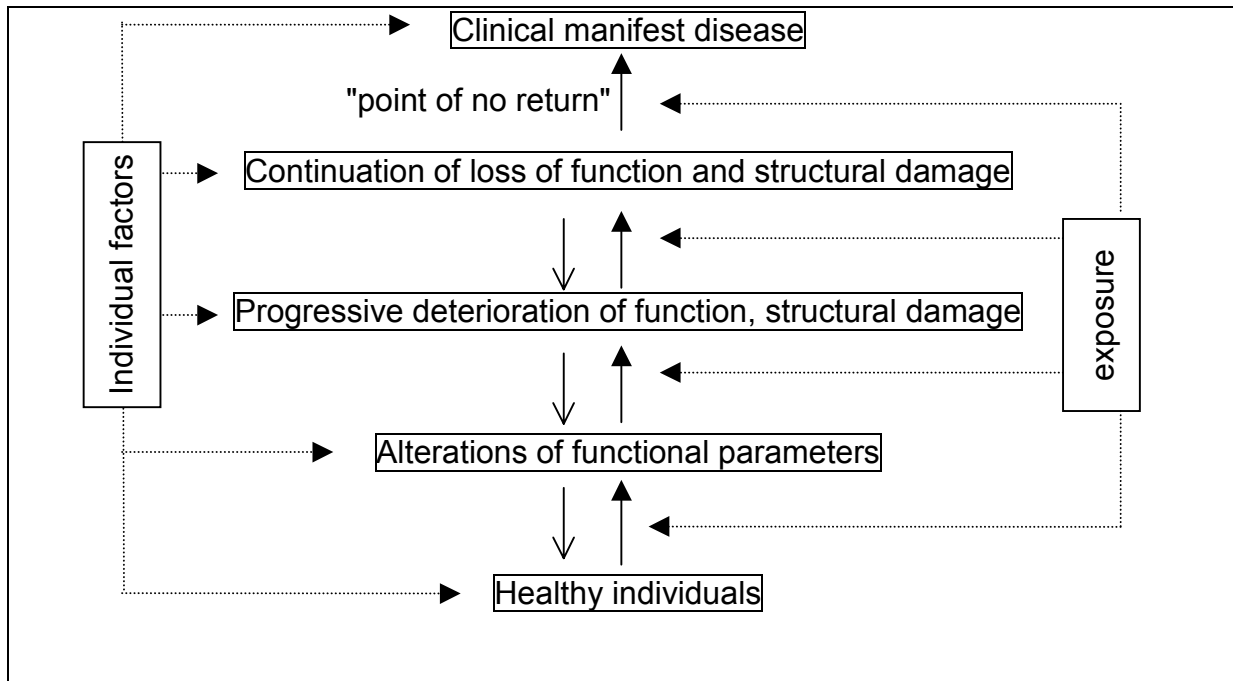
Under conditions of chronic solvent exposure to lower concentrations, renal damage may remain clinically silent for many years due to the large functional reserve capacity of the kidney. During this time, alterations may gradually progress through a cascade of events from early biological effects which may be of no clinical significance through initially reversible functional and/or structural alterations to focal damage and finally to manifest, clinically detectable disease (Fig. 4.1) (MUELLER et al., 1997a; PRICE et al., 1996). The detection of such alterations before the onset of irreversible and perhaps further progressing clinical changes requires the use of sensitive, reliable indicators ("biomarkers of effect"). In epidemiological studies, these indicators may be used for detecting groups which are potentially at risk, even when the pathological significance and the predictive value of these "early" indicators are frequently unknown (BERNARD and LAUWERYS, 1989; LISON, 1989) and further investigations are necessary.

The diagnostic parameters which have been used in epidemiological and occupational medicine studies on workers exposed to known or suspected nephrotoxins are summarized in Tab. 4.1. For more details see overviews from BERNARD and LAUWERYS (1991), BERNDT (1981), BOEGE (1998) LAUWERYS and BERNARD, (1989), LAUWERYS et al., (1992), MUTTI (1989). Control values from controlled studies are compiled in Tab. 4.2.

Proteinuria, i.e. the increased excretion of proteins in the urine, is a common characteristic of most functional alterations or diseases of the kidney. Functional alterations may affect either the glomerular filtration system or the renal interstitium with the tubular system, or both components.

However, though most toxic effects on the kidney and kidney diseases are associated with an increased excretion of certain proteins in urine, one has to keep in mind that some other, pathological and non-pathological processes may also cause temporary or persistent proteinuria, e.g. certain systemic diseases (especially diabetes and hypertension) and psychological or physical stress ("horse-race effect")

including possibly shift-work (BOEGE, 1998; BOOGAARD and CAUBO, 1994; KANNEL et al., 1984).



**Fig. 4.1** Simplified flow chart of cascade of events following exposure to renal toxins (adapted with modifications from PRICE et al., 1996; MUELLER et al., 1997a). Dashed lines indicate influence of exposure and individual factors (e.g. susceptibility, other diseases), solid bold lines indicate progression of renal functional and structural alterations to disease; solid thin lines indicate improvement after ceasing exposure.

The concentration of proteins in urine is usually given either as mass or enzyme activity per volume or related to creatinine (mass or activity per g or per mmol creatinine). The urinary creatinine content reflects the degree of urinary concentration and can thus be used to correct mathematically for the effects of diuresis and antidiuresis (BOEGE, 1998; JUNG, 1991; NEWMAN et al., 2000). Sometimes excretion rates (mass or activity/time) are given, which need, however, more effort to measure in contrast to more easily obtained spot samples.

Correction for urinary flow may be obtained by using creatinine in urine as reference and is recommended for all parameters described below. Creatinine excretion is related to muscle mass and in adults thus decreases with age (THOMAS, 1998c). Therefore, for all parameters described below values should be compared to age matched controls (PRICE, 1982, 1992). Correction factors for age are available for albumin (Tab. 4.2) (WATTS et al., 1982). As a rough estimate they may be applied to other urine parameters as well.

An overview on types of kidney dysfunction and corresponding markers is given in Tab. 4.3. The integrity of the glomerular filtration barrier may be assessed by evaluating its selective permeability to blood constituents, namely high-molecular-

weight proteins, which are physiologically restricted to the vascular compartment. One of the main functions of the proximal tubuli, their absorptive ability, may be evaluated by measuring the urinary excretion of low-molecular-weight proteins. Furthermore, tissue constituents may be shed into urine following toxic damage to specific structures. Within certain limits, therefore the pattern of the excreted proteins allows deductions to be made with respect to the type and location of the effect, whereas the amount of marker proteins which are excreted correlates with the extent of alteration or disease (BOEGE, 1998).

Rather than assessing one single parameter attempts have been made to identify suitable test batteries (MUTTI et al., 1992; MUELLER et al., 1997b; PRICE et al., 1997).

Tab. 4.1 Markers for detection of renal functional alterations

| Parameter       | Indicator for alteration of | Test method  | Normal range*                                 | Detection limit   | Remarks  | Reference                     |
|-----------------|-----------------------------|--|---|---|--|-------------------------------|
| <b>In urine</b> |                             |  |   |   |  |                               |
| Total protein   | Glomerular filtration       |  | Depending on test method                      |   |  |                               |
|                 |                             | Test strip, protein sensitivity of pH-dye indicator, colorimetry | –   | Variable, e.g.:<br>+ reaction at > 200 mg/l<br>– reaction at < 150 mg/l | Response mainly to albumin and transferrin; semi-quantitative determination; no reaction at normal urinary protein excretion | GUDER (1987);<br>BOEGE (1998) |
|                 |                             | Biuret, photometry   | ≤ 150 mg/24 h                                 | ca. 100 mg/l  |  | GUDER (1987)                  |
|                 |                             | TCA, turbidimetry  | ≤ 70 mg/24 h                                  | ca. 30 mg/l   |  | GUDER (1987)                  |
| Albumin         | Glomerular filtration       |  | 6.4 – 19.2 mg/l<br>6.5 – 37.1 mg/g creatinine |   | Influenced by orthostatic position or high levels of physical activity   | BOEGE (1998)                  |
|                 |                             | Dip stick  |   | 150 – 300 mg/l  |  | HASHIMOTO et al. (1991)       |
|                 |                             | Special test strip, dye indicator or immunoassay                 |   | 20 mg/l   | Suitable for exclusion of "microalbuminuria"   | BOEGE (1998)                  |
|                 |                             | Various immunochemical tests                                     |   | 0.8 – 8.5 mg/l  |  | BOEGE (1998)                  |
|                 |                             | Turbidimetry   |   | Within normal range   |  | GUDER (1987)                  |
| Transferrin     | Glomerular filtration       | Immunonephelometry   | 0.2 – 1.2 mg/l<br>0.1 – 1.9 mg/g creatinine   | 0.2 mg/l (analytical sensitivity)                                       |  | BOEGE (1998)                  |

| Parameter                                 | Indicator for alteration of               | Test method                            | Normal range*   | Detection limit                         | Remarks  | Reference                                    |
|---|---|--|---|---|--|--|
| <b>In urine</b>                           |   |  |   |   |  |  |
| IgG                                       | Glomerular filtration                     | Immunonephelometry, immunoturbidimetry | 0.8 – 2.9 mg/l<br>0.8 – 5.73 mg/g creatinine  | 1 mg/l (analytical sensitivity)         |  | BOEGE (1998)                                 |
| $\beta_2$ -microglobulin ( $\beta_2$ M)   | Tubular reabsorption                      | Special immunoassays                   | $\leq 0.3$ mg/l<br>0.2 mg/g creatinine  | 0.1 – 0.2 mg/l (analytical sensitivity) | Unstable at pH <6; simultaneous determination in serum allows for calculation of $\beta_2$ M-clearance | BOEGE (1998)                                 |
| $\alpha_1$ -microglobulin ( $\alpha_1$ M) | Tubular reabsorption                      | Immunonephelometry, immunoturbidimetry | $\leq 11.2$ mg/g creat. (18 – 40 a)<br>$\leq 19.4$ mg/g creat. (> 40 a)<br>$\leq 12$ mg/l<br>20 mg/24 h | 1 – 3.5 mg/l (analytical sensitivity)   |  | BOEGE (1998)                                 |
| Retinol binding protein (RBP)             | Tubular reabsorption                      | Immunonephelometry                     | < 0.5 mg/l  | 1.2 mg/l (analytical sensitivity)       |  | BOEGE (1998)                                 |
| Fibronectin                               | Part of glomerulus, glomerular filtration | ELISA<br>RIA                           | 14.8 $\mu$ g/g creatinine (mean)  | Not reported                            | Elevated before onset of microalbuminuria, i.e. altered glomerular permeability                        | PRICE et al. (1997);<br>TAYLOR et al. (1987) |
| Laminin                                   | Glomerular/ tubular basement membrane     |  | Not yet established   | Not reported                            | Fragments of the compound detectable in urine  | PRICE et al. (1997)                          |

| Parameter                          | Indicator for alteration of | Test method   | Normal range*  | Detection limit | Remarks  | Reference                        |
|------------------------------------|-----------------------------|---|--|-----------------|--|----------------------------------|
| <b>In urine</b>                    |                             |   |  |                 |  |                                  |
| Alkaline phosphatase               | Tubular integrity           | Photometry (4-nitro-phenylphosphate as substrate)                                   | < 14 U/g creatinine (97.5 percentile; 23 – 58 a)   | Not reported    | Enzyme of proximal tubular brush-border  | JUNG et al. (1990)               |
| N-acetyl-β-D-glucosaminidase (NAG) | Tubular integrity           | Photometry (4-nitro-phenyl-N-acetyl-β-D-glucosaminide or as substrate) <sup>a</sup> | ≤ 6.3 U/l<br>≤ 5 U/g creatinine*<br>< 5.8 U/g creatinine (97.5 percentile; 23 – 58 a, men)<br>< 8.2 U/g creatinine (97.5 percentile; 23 – 58 a, women) | Not reported    | Enzyme of lysosomes of proximal tubular brush-border, increased activity in pregnant women (PRICE, 1992) | BOEGE (1998); JUNG et al. (1990) |
| Alanine amino-peptidase (AAP)      | Tubular integrity           | Photometry (aniline-4-nitroanilide as substrate)                                    | < 19.4 U/g creatinine (97.5 percentile; 23 – 58 a)   | Not reported    | Enzyme of proximal tubular brush-border  | JUNG et al. (1990)               |

\* Data refer to adults, if not indicated otherwise; note: normal ranges and reference values may vary depending on the laboratory and test conditions.

a: Another test substrate is the 3,3'-dichlorophenyl sulfonylphthalein derivative of N-acetyl-β-D-glucosaminide (BOEGE, 1998).

| Parameter                               | Indicator for alteration of      | Test method                            | Normal range*                                   | Detection limit    | Remarks  | Reference                                |
|---|----------------------------------|--|---|--------------------|--|--|
| <b>In serum</b>                         |                                  |  |   |                    |  |  |
| Creatinine                              | glomerular filtration rate (GFR) |  | depending on test method                        |                    |  |  |
|   |                                  | Jaffe-reaction, photometry             | men: 7 – 12 mg/l<br>women: 6 – 11 mg/l          | Below normal range | Large interindividual variation; only pronounced (> 50 %) reduction of GFR detectable (large "creatinine-blind range") determining only advanced disease | GUDER (1987)                             |
|   |                                  | Enzymatic reaction, photometry         | men: 5.5 – 11 mg/l<br>women: 4.9 – 9 mg/l       |                    |  |  |
| $\beta_2$ -microglobulin ( $\beta_2M$ ) | GFR                              | Special immunoassays                   | 0.8 – 2.4 mg/l ( $\leq 60$ a)                   | Not reported       | More sensitive marker than serum creatinine  | THOMAS (1998e)                           |
| Cystatin C (clara cell protein)         | GFR                              | Immunonephelometry, immunoturbidimetry | 0.6 – 1.22 mg/l<br>0.7 – 1.6 mg/l (two studies) | Not reported       | More sensitive marker than serum creatinine  | THOMAS (1998h);<br>BERNARD et al. (1997) |

| Parameter                          | Indicator for alteration of      | Test method     | Normal range*                                  | Detection limit | Remarks   | Reference    |
|------------------------------------|----------------------------------|-----------------|--|-----------------|---|--------------|
| <b>Combined serum/urine</b>        |                                  |                 |  |                 |   |              |
|                                    | Glomerular filtration rate (GFR) |                 |  |                 | Decline with age, influenced by physical effort, hydration state, body surface area |              |
| Creatinine clearance               |                                  | See creatinine  | Men: 80 – 160 ml/min<br>women: 75 – 130 ml/min | -               |   | GUDER (1987) |
| $\beta_2$ -microglobulin clearance |                                  | See $\beta_2$ M | 0.03 – 0.12 ml/min                             | -               |   | BOEGE (1998) |



**Tab. 4.2** Normal values for various biomarkers of renal function in humans  
(for abbreviations, see list in chapter 9.2)

| Reference                                  |                      | TAYLOR et al. (1997)   |      |        | MUTTI et al. (1992)                                      |                 |      | BERNARD and LAUWERYS (1991)  |                                   |    |
|--|----------------------|--|------|--------|--|-----------------|------|------------------------------|-----------------------------------|----|
| Type of sample                             |                      | Non-exposed male controls after application of cut-off value |      |        | General population 18 – 65 a, no renal disease, no drugs |                 |      | Male subjects, age 30 – 60 a |                                   |    |
| No. of samples                             |                      | 206-260  |      |        | 300  |                 |      | 100                          |                                   |    |
| Biomarker                                  | Unit                 | Mean   | SD   | UL*    | Mean <sup>g</sup>  | SD <sup>g</sup> | UL   | Median                       | 5th – 95 <sup>th</sup> percentile | UL |
| <b>In urine</b>                            |                      |  |      |        |  |                 |      |                              |                                   |    |
| Total protein                              | mg/g creatinine      | 57.5   | 25.8 | 161    |  |                 |      |                              |                                   |    |
| Albumin                                    | mg/g creatinine      | 5.36   | 2.72 | 17.6   | 5.1  | 1.79            | 19.5 | 5.2                          | 2.8 – 15                          |    |
| $\beta_2$ M                                | $\mu$ g/g creatinine | 59.4   | 36.2 | 209    | 97.7   | 2.14            | 423  | 62                           | 21 – 142                          |    |
| BB <sub>50</sub>                           | U/g creatinine       | 7.8  | 5.93 | 34.0   |  |                 |      |                              |                                   |    |
| BBA  | U/g creatinine       | 5.39   | 4.29 | 24.5   | 3.5  | 1.75            | 12.9 |                              |                                   |    |
| Fibronectin                                | $\mu$ g/g creatinine | 14.8   | 7.85 | 49.9   |  |                 |      |                              |                                   |    |
| GAG  | mg/g creatinine      | 33.2   | 9.80 | 74.3   |  |                 |      |                              |                                   |    |
| HF5  | U/g creatinine       | 5.47   | 3.86 | 22.0   |  |                 |      |                              |                                   |    |
| IAP  | U/g creatinine       | 0.54   | 0.43 | 2.21   |  |                 |      |                              |                                   |    |
| IgG  | $\mu$ g/g creatinine | 1007.0   | 666  | 3857.0 | 653  | 1.87            | 2613 | 1200                         | 350 – 2700                        |    |
| 6-keto PGF <sub>1<math>\alpha</math></sub> | ng/g creatinine      | 155.0  | 57.8 | 416.0  |  |                 |      |                              |                                   |    |
| Lysozyme                                   | $\mu$ g/l            |  |      |        |  |                 |      | 15                           | 2 – 12                            |    |
| NAG  | U/g creatinine       | 1.38   | 0.73 | 4.64   |  |                 |      |                              |                                   |    |
| NSAP                                       | U/g creatinine       | 0.34   | 0.03 | 1.65   |  |                 |      |                              |                                   |    |
| PGE <sub>2</sub>                           | ng/g creatinine      | 123.0  | 95.8 | 549.0  |  |                 |      |                              |                                   |    |

| Reference         |                 | TAYLOR et al. (1997)   |      |        | MUTTI et al. (1992)                                      |                 |      | BERNARD and LAUWERYS (1991)  |                                   |    |
|-------------------|-----------------|--|------|--------|--|-----------------|------|------------------------------|-----------------------------------|----|
| Type of sample    |                 | Non-exposed male controls after application of cut-off value |      |        | General population 18 – 65 a, no renal disease, no drugs |                 |      | Male subjects, age 30 – 60 a |                                   |    |
| No. of samples    |                 | 206-260  |      |        | 300  |                 |      | 100                          |                                   |    |
| Biomarker         | Unit            | Mean   | SD   | UL*    | Mean <sup>g</sup>  | SD <sup>g</sup> | UL   | Median                       | 5th – 95 <sup>th</sup> percentile | UL |
| PGF <sub>2α</sub> | ng/g creatinine | 279.0  | 177  | 1023.0 |  |                 |      |                              |                                   |    |
| RBP               | µg/g creatinine | 62.8   | 29.9 | 189.0  | 38.1   | 1.99            | 154  | 55                           | 30 – 130                          |    |
| THG               | mg/g creatinine | 16.4   | 9.54 | 56.2   | 16.7   | 1.79            | 64   | 14.3                         | 5.1 – 25.5                        |    |
| TRF               | µg/g creatinine | 202.0  | 155  | 832    | 240  | 2.15            | 1101 | 170                          | 80 – 830                          |    |
| TXB <sub>2</sub>  | ng/g creatinine | 50.0   | 26.0 | 151    |  |                 |      |                              |                                   |    |
| <b>In serum</b>   |                 |  |      |        |  |                 |      |                              |                                   |    |
| AGBM              | Arbitrary       | 25.1   | 7.50 | 56.0   |  |                 |      |                              |                                   |    |
| β <sub>2</sub> M  | mg/l            | 1.38   | 0.32 | 2.67   |  |                 |      |                              |                                   |    |

SD standard deviation

\*: calculated as 3rd quartile values plus three times the interquartile range

g geometric mean and geometric-SD

**Tab. 4.3** Types of toxic kidney damage and corresponding markers (BERNARD and LAUWERYYS, 1991; BOEGE, 1998; DUBACH et al., 1988; MUTTI, 1999; PRICE et al., 1996; PRICE, 2000)

| Location of damage | Effect   | Markers in urine <sup>a</sup>  |   |
|--------------------|--|--|---|
| Glomerular         | Destruction of matrix: release of basement membrane and extracellular matrix components  | Laminin, Type IV collagen and their fragments; fibronectin, sialic acids, prostanoids: TXB <sub>2</sub> ; 6-keto-PGF <sub>1α</sub> |   |
|                    | Selective: increased permeability for midsize anionic proteins   | Albumin, transferrin, (0.03 – 0.3 g protein /d)  |   |
|                    | Non-selective: increased permeability for large molecules and cells  | Albumin, IgG (1.5 , 20 g/d), erythrocytes, lymphocytes   |   |
|                    | Function: filtration decreased   | Creatinine clearance, inulin clearance, <sup>51</sup> Cr-EDTA clearance  |   |
| Mixed              | Increased glomerular permeability for high molecular proteins: secondary damage or saturation (overflow proteinuria) of tubular reabsorption | Albumin, α <sub>1</sub> M, total protein   |   |
| Tubular            | Function: affected concentrating ability   | Concentrating ability (specific density)   |   |
|                    | Decreased reabsorption of low-molecular proteins   | α <sub>1</sub> M, β <sub>2</sub> M, RBP  |   |
|                    | Injury of tubuli:  | distal tubule  | Kallikrein                                  |
|                    |  | loop of Henle  | Tamm-Horsfall glycoprotein                  |
|                    |  | collecting tubule and interstitium   | PGF <sub>2α</sub> , PGE <sub>2</sub>        |
|                    |  | site unrelated   | GAG   |
|                    | Cell injury: excretion of renal antigens   | BB50, BBA, HF5, IAP  |   |
|                    | Cell injury: enzyme excretion  | brush border   | Alkaline phosphatase, aminopeptidases       |
|                    |  | lysosomes  | N-acetyl-β-glucosaminidase, β-galactosidase |
|                    |  | cytosol  | β-glucosidase, ligandin, LDH                |
| proximal tubule    |  | Ligandin, alkaline phosphatase, aminopeptidases  |   |
| distal tubule      |  | LDH (also present in other nephron parts)  |   |

a: except for clearance, which is calculated from concentration of marker in blood and urine

## **4.2 Selected parameters as biomarkers for solvent induced renal alterations**

In this chapter the most important biomarkers are described. Most information on the general properties of these biomarkers comes from reviews, especially BERNARD and LAUWERYS (1991); BOEGE (1998); LAUWERYS and BERNARD, (1989); LAUWERYS et al. (1992); MUTTI (1989); PISCATOR (1989); PRICE (1982, 1992); TAYLOR et al. (1997). Control values for these markers have been compiled in Tab. 4.2.

### **4.2.1 Total protein**

Determination of the total protein content of urine has formerly been recommended as one of the most useful tests in diagnosis of renal disease. However, precision of conventional laboratory quantitation of total protein in urine of healthy individuals has been reported to be poor (CHAMBERS et al., 1989).

Plasma proteins account for about 25 % of the total proteins in urine. The major portion of total proteins in normal urine consists of renal structural proteins and secretory tubular proteins, half of which comprise Tamm Horsfall glycoprotein and secretory IgA (BOEGE, 1998).

Test strip analysis is widely used as a screening method for the detection of protein in urine. These tests are based on the altered pH-sensitivity of dye indicators due to the presence of protein. The reaction, and therefore the sensitivity, varies depending on the nature of the proteins present, the sensitivity for albumin being higher than for other urinary proteins. The detection limit of these conventional dipsticks is between 150 and 300 mg/l (BOEGE, 1998; HASHIMOTO et al., 1991).

Pathological processes may, at an early stage, affect the urinary excretion of individual proteins selectively, without significantly changing the total protein excretion. Hence, it is preferable to measure the urinary excretion of specific proteins that are representative of either the high-molecular-weight or the low-molecular weight group rather than total protein excretion.

### **4.2.2 Albumin**

Due to its high molecular weight (MG 68000) and strong overall negative charge, only minute quantities of albumin normally cross the glomerular filter. Therefore, an increase in albumin in the urine usually results from an increased glomerular permeability to albumin. However, it may also be caused by reduced tubular absorption of the filtered load (VERPLANKE and HERBER (1998). This can be easily ruled out, if the increase of albumin in urine occurs without significant changes in the urinary concentration of low molecular weight proteins which are markers of tubular defects.

A false positive increase of albumin in urine of women may occur from contamination with menstrual blood (HOTZ, 1994).

The increased albuminuria observed in diabetics and in minimal-change nephropathy might result partly from the preferential filtration of abnormal forms of albumin. It has not yet been assessed whether xenobiotics or their metabolites which bind to

albumin may lead to abnormal forms of albumin and modify its filtration by this mechanism (BERNARD and LAUWERYS, 1991; LAUWERYS and BERNARD, 1989).

Albumin is quantitatively the major urinary protein derived from plasma. Its concentration in normal urine is on the average at least five times higher than that of other high molecular weight proteins. Albumin is therefore the most easily quantifiable protein in urine.

"Microalbuminuria" ("paucialbuminuria") (Tab. 4.1) is defined as urinary excretion of albumin that is persistently increased above normal but below the sensitivity of conventional semiquantitative test strips for protein in urine (see 4.2.1) which detect only higher albumin values ("macroalbuminuria"). However, special test strips (e.g. Micral-Test®) are available for the semi-quantitative measurement of microalbuminuria (ADAMSON et al., 1993). Also, albumin can easily be analysed in unconcentrated normal urine with routine methods using very sensitive immunoassays (BOEGE, 1998; WATTS et al., 1988). Albumin is also readily detectable by most electrophoretic and chromatographic methods (BERNARD and LAUWERYS, 1991).

**Tab. 4.1** Classification and cut-off limits of albuminuria (BOEGE, 1998)

| Status           | $\mu\text{g}/\text{min}^{\text{a}}$ | $\text{mg}/24 \text{ h}^{\text{b}}$ | $\text{mg}/\text{l urine}^{\text{c}}$ | $\text{mg}/\text{g creatinine}^{\text{d}}$ |
|------------------|-------------------------------------|-------------------------------------|---------------------------------------|--|
| Normal           | < 20                                | < 30                                | < 20                                  | < 24                                       |
| Microalbuminuria | 20 – 200                            | 30 – 300                            | 20 – 200                              | 24 – 200                                   |
| Macroalbuminuria | > 200                               | < 300                               | > 200                                 | > 200                                      |

a: collection of urine limited to a specified period of time, e.g. from 8 – 10 a.m.; b: 24 h-urine collection;  
c: first morning spot urine; d: second morning spot urine

Intraindividual variability of albumin urine concentrations is high (NEWMAN et al., 2000; STENGEL et al., 1999; WATTS et al., 1988). According to WATTS et al. (1988), it is about 100 % and comparable for albumin concentration, albumin/creatinine ratio and albumin excretion rate.

Albumin may be increased due to orthostatic position (BERNARD and LAUWERYS, 1991; VERPLANKE and HERBER, 1998). Overnight values are lower than daytime values, the latter being about 5 mg/g creatinine. The highest values are about five times higher and correspond to the highest normal value of 20 mg/g creatinine (see Tab. 4.1). An increased albuminuria is also well-known in subjects with systolic and/or diastolic blood pressure  $\geq 140/90$  mmHg (GOSLING and BEEVERS, 1989).

Microalbuminuria is indicative of stage III nephropathy in diabetics which may occur 10 to 15 years after diabetes has been diagnosed (BOEGE, 1998).

A relationship between microalbuminuria and cardiovascular risk factors such as mean systolic blood pressure, obesity, hyperlipidemia, alcohol consumption, and smoking, but also factors of peripher insulin resistance, has been shown in extensive studies involving clinically healthy persons as well as elderly and young patients with hypertension undergoing antihypertensive therapy. It is unclear whether microalbuminuria in these patients is an early indicator of glomerular nephropathy, a con-

sequence of increased renal perfusion, or if it reflects impaired endothelial function. However, microalbuminuria is considered by itself as another cardiovascular risk factor (BOEGE, 1998).

Albumin excretion increases with age (STENGEL et al., 1999; WATTS et al., 1988). According to WATTS et al. (1988), this is due to reduced urinary flow; if albumin concentrations are given as albumin/creatinine ratio, the influence disappears. On the other hand, an increased prevalence of a high urinary albumin excretion has been found in apparently healthy adolescents (< 20 a of age), the reasons for this phenomenon are unknown at present (BERNARD et al., 1997).

Cigarette smoking is found to be significantly associated with slight albuminuria, consistent with its role as an index of risk of cardiovascular disease (METCALF et al., 1993).

A positive relation between alcohol consumption on the day before investigation and the renal excretion rate of albumin was found in the studies of KRUSELL et al. (1985) and METCALF et al. (1993). However, STENGEL et al. (1999) found no such association.

In the general population, albumin values are less than a factor of two higher in daytime than in overnight samples (Tab. 4.3) (WATTS et al., 1988). Similarly, in a study albumin values were higher in end-of-shift urine samples than in overnight urine samples by a factor of less than two. This relation was similar in controls (working in factory producing cardboard boxes) as in the exposed group (working in yacht manufacturing) (VERPLANKE and HERBER, 1998). No difference in albumin excretion was found in the study of VIAU et al. (1987) in urine samples collected upon arrival at work on the first day of the work as well as in the mean of all samples collected during the work week, both in control and in exposed workers.

Exercise is known to increase albumin concentration in urine. For example, NEWMAN et al. (2000) found an increase in the mean values from 18.2 before to 295.0 mg/l (average gain was 110.6 mg/l) after a two hour game in American football players. However, such an increase due to vigorous exercise is at least partially due to water loss and reduced urine flow as indicated by a concomitant rise in osmolality and in creatinine concentration. When albumin excretion was corrected for creatinine in the study of NEWMAN et al. (2000), the effect of exercise was much reduced. Albumin/creatinine ratio rose from a mean of 6.7 mg/g creatinine before the game to a mean of 37.9 mg/g postgame with a maximum of 109 mg/g. The albumin/creatinine ratio was not significantly different between pre- and postgame values.

BOOGAARD and CAUBO (1994) found that albumin was significantly higher in control shift workers than in control day workers, the median concentration being 5.7 instead of 4.7 mg/g creatinine. This may reflect differences in albumin concentrations in daytime samples compared to overnight samples as shown in Tab. 4.3. Values may also be different due to differences in physical activity in both groups, as described above.

**Tab. 4.2** Estimates of independent effects of sex, age, mean arterial blood pressure (MABP) and surface area (SA) on overnight recumbent (OR) and daytime ambulant (DA) urine albumin excretion in 127 healthy subjects (data from WATTS et al., 1988)

| Urine collection conditions | Albumin excretion rate         | Associated multiplying factor on albumin excretion variables |                       |                           |  |
|-----------------------------|--------------------------------|--|-----------------------|---------------------------|--|
|                             |                                | Female sex   | 10 yr increase in age | 10 mm Hg increase in MABP | 0.1m <sup>2</sup> increase in surface area |
| OR                          | U <sub>A</sub>                 | 0.83   | 0.80**                | 1.08                      | 0.98                                       |
| OR                          | U <sub>A</sub> /U <sub>C</sub> | 1.07   | 0.98                  | 0.96                      | 0.95*                                      |
| OR                          | U <sub>AV</sub>                | 0.84   | 0.99                  | 1.00                      | 1.01                                       |
| DA                          | U <sub>A</sub>                 | 1.17   | 0.80**                | 0.95                      | 1.05                                       |
| DA                          | U <sub>A</sub> /U <sub>C</sub> | 1.14   | 0.93                  | 0.99                      | 0.94*                                      |
| DA                          | U <sub>AV</sub>                | 0.80   | 1.00                  | 0.91                      | 0.90                                       |

U<sub>A</sub>: albumin concentration (mg/l) ;

U<sub>A</sub>/U<sub>C</sub>: albumin/creatinine ratio (mg/mmol);

U<sub>AV</sub>: albumin excretion rate (µg/min).

\*p < 0.05 ; \*\* p < 0.01.

**Tab. 4.3** Control values for albumin excretion in the general population

| Time of sampling | Geometric mean      | Median              | Range                      | Reference                   |
|------------------|---------------------|---------------------|----------------------------|-----------------------------|
| Not specified    |                     |                     | 6.4 – 19.2 mg/l            | BOEGE, 1998                 |
| Overnight        | 3.9 mg/l            |                     | 0.9 – 16.2 mg/l            | WATTS et al. (1988)         |
| Daytime          | 5.1 mg/l            |                     | 0.0 – 29.6 mg/l            | WATTS et al. (1988)         |
| Not specified    |                     |                     | 6.5 – 37.1 mg/g creatinine | BOEGE, 1998                 |
| Not specified    |                     | 5.2 mg/g creatinine | 2.8 – 15 mg/g creatinine   | BERNARD and LAUWERYS (1991) |
| Overnight        | 3.5 mg/g creatinine |                     | 0.9 – 9 mg/g creatinine    | WATTS et al. (1988)         |
| Daytime          | 5.3 mg/g creatinine |                     | 0.9 – 20.3 mg/g creatinine | WATTS et al. (1988)         |

### 4.2.3 Transferrin

The major interest of urinary transferrin is that it appears to be a more sensitive indicator of glomerular changes than albumin in some glomerulopathies (LAUWERYS et al., 1992).

Transferrin is a protein similar in size to but less anionic than albumin. Transferrinuria precedes microalbuminuria in patients with diabetic nephropathy and may either suggest early changes in the polyanionic glomerular basement barrier or altered

tubular handling of these proteins (YAQOOB et al., 1993b). For example, an elevated urinary excretion of albumin or transferrin is usually regarded as an indicator of an increased glomerular permeability due to changes of the polyanionic glomerular basement membrane barrier (BERNARD and LAUWERYS, 1989; VIAU et al., 1987).

#### 4.2.4 IgG

An increase in the urinary excretion of IgG is viewed as an index of more serious glomerular lesions in cases of a non-selective glomerular proteinuria. IgG crosses the glomerular filter mainly via the small population of large pores (effective radius > 5 nm) called a shunt pathway (BERNARD and LAUWERYS, 1991). Consequently, IgG has been proposed as an index for evaluating the extent of the shunt pathway. An IgG/albumin ratio of < 0.03 indicates selective, a ratio > 0.03 non-selective glomerular proteinuria (BOEGE, 1998).

#### 4.2.5 $\beta_2$ -Microglobulin

$\beta_2$ -microglobulin ( $\beta_2$ M) is a small protein with a molecular weight of 11800. It is present at the cell membrane as part of the histocompatibility antigens. Healthy subjects excrete around 70 to 80  $\mu$ g/24 h on the average, but excretion is enhanced in case of renal tubular impairment (BERNARD and LAUWERYS, 1991).

One advantage of  $\beta_2$ M is that the relative clearance can be estimated if the protein is also determined in serum.

The high sensitivity of this parameter to proximal tubular insult results from the fact that under normal conditions its reabsorption is nearly complete (99.97 %) (BERNARD and LAUWERYS, 1991; PISCATOR, 1989). A decrease of 0.1 % in reabsorption capacity thus results in a threefold increase in  $\beta_2$ M excretion in urine (PISCATOR, 1989).

The determination of urinary  $\beta_2$ M has been widely used for the screening of proximal tubular damage (BERNARD and LAUWERYS, 1991). The major disadvantage of measuring  $\beta_2$ M is its instability in acid urine. At a urinary pH < 5.5, a time- and temperature-dependent degradation of  $\beta_2$ M occurs. This degradation is very rapid at 37 °C and thus may already occur in the bladder, so that even neutralization of the urine immediately after collection does not solve the problem (BERNARD and LAUWERYS, 1981; VIAU et al., 1987). For  $\beta_2$ M to be a reliable indicator of proximal tubular function, the urine specimen should be collected several hours after ingestion of sodium hydrogencarbonate, a procedure which clearly is not feasible in monitoring populations at risk in industry or in the environment (BERNARD and LAUWERYS, 1991; MUTTI, 1989; PISCATOR, 1989).

#### 4.2.6 Retinol-binding protein

The function of retinol-binding protein (RBP, also called  $\alpha_2$ -microglobulin) is to transport vitamin A from the liver to epithelial tissues in form of a trimolecular complex of RBP, retinal and transthyretin. The size of this trimolecular complex is sufficient to prevent its elimination in urine. Free RBP with a molecular weight of



2100 is rapidly eliminated from plasma by glomerular filtration, then reabsorbed and catabolized by proximal tubular cells (BERNARD and LAUWERYS, 1991).

The renal handling of RBP is very similar to that of  $\beta_2$ -microglobulin in that it is also reabsorbed by proximal tubular cells with an efficiency of about 99.97 %. Both proteins compete for their uptake by the kidney. In contrast to  $\beta_2$ M, RBP is stable in acid urine and requires no precaution for the collection of the urine sample (BERNARD and LAUWERYS, 1991).

There are no other known reasons than renal insufficiency for increased levels of RBP. According to MUTTI (1989), however, increased RBP concentrations may also result from competition of some cationic substances with RBP for tubular reabsorption, but repeated measurements are assumed to be sufficient to rule out this interference.

#### **4.2.7 N-acetyl- $\beta$ -D-glucosaminidase**

Although the presence of enzymes in urine has been known for a considerable time, their use as diagnostic indicators has received little attention compared to that given to serum enzymes. The principal reason for the slow development of this field is the difficulty involved in the assay of enzymes in a fluid which varies in volume and composition, and which is a hostile environment for many enzymes. A large number of enzymes are excreted in urine but few are suitable for diagnostic purposes. Of these, probably the most widely studied is N-acetyl- $\beta$ -D-glucosaminidase (NAG).

NAG is an enzyme located in the lysosomes of renal tubular cells which plays a role in the breakdown of glycoproteins. It has a high molecular weight (130 000 to 140 000) and therefore is not normally filtered at the glomerulus. Low levels of NAG found in normal urine result from the normal exocytosis and pinocytotic activity of the epithelial cells (PRICE; 1992; VYSKOCIL et al., 1991). Several isoenzymic forms of NAG exist, which enhances its diagnostic potential as they may occur in different ratios in diseases. Isoenzyme B increases usually with damage (PRICE, 1992), the serum A<sup>s</sup>-form is present due to glomerular damage in Goodpasture's syndrome (PRICE, 1982).

NAG has been shown to be a sensitive indicator of early renal tubular injury. A consistent elevation of urinary NAG is always associated with progressive renal damage. Increases are reversible after recovery from disease (PRICE, 1982).

The activity of NAG in urine seems to be a less sensitive indicator of renal tubular damage than RBP or  $\beta_2$ M (LAUWERYS and BERNARD, 1989). Abnormal NAG values usually are observed when the RBP concentration in urine already exceeds the normal level by a factor of 100 or more.

Unlike many other urinary enzymes, NAG is especially resistant to degradation (MEYER et al., 1985; PRICE, 1992). However, NAG undergoes some degradation when samples are frozen, therefore storage at 4°C is preferred (VIAU et al., 1987).

NAG can be assayed easily and reproducibly by colorimetric assays (MEYER et al., 1985; PRICE, 1992). The relatively small variation of NAG is an advantageous pro-

perty of this enzyme in comparison with other urinary enzymes with larger preanalytical variations, favouring its clinical usefulness. The second sample of the day has proved to be the most reliable for analysis (JUNG, 1991).

The intraindividual variability of NAG measurements is high and in the same order of magnitude as the interindividual variability (STENGEL et al., 1999; WATTS et al., 1988). NAG excretion does not differ between men and women according to PRICE (1992) and (VERPLANKE and HERBER, 1998), but JUNG et al. (1990) found that for adults between 23 and 58 years of age the upper limit of NAG-activity (97.5<sup>th</sup> percentiles) was higher in women than in men. STENGEL et al. (1999) reported that NAG excretion is significantly and positively associated with age, smoking, alcohol consumption, and body-mass index. However, in a large collaborative study conducted in five European countries, no significant effect of smoking was observed (TAYLOR et al., 1997).

#### **4.2.8 Alanine aminopeptidase, $\beta$ -galactosidase, and $\beta$ -glucuronidase, leucine aminopeptidase, alkaline phosphatase**

Alanine aminopeptidase (AAP) and several other enzymes such as  $\beta$ -galactosidase ( $\beta$ Gal),  $\beta$ -glucuronidase ( $\beta$ Glu), leucine aminopeptidase (LAP), and alkaline phosphatase (AP) are further markers of tubular damage. Especially, AAP has become important as diagnostic marker in clinical acute tubular necrosis and toxic tubular damage (HÖRL, 1994). AAP correlated with age and alcohol consumption (STENGEL et al., 1999). The interindividual and intraindividual variation is high.

#### **4.2.9 Lysozyme**

Lysozyme (muraminidase) is an enzyme originating from phagocytic cells that catalyses the hydrolysis of the peptidoglycane layer of bacterial cell walls. The urinary excretion of this enzyme increases during urinary tract infections, proximal tubular damage, and excessive endogenous synthesis which exceeds the absorption capacity of the proximal tubulus. Therefore, an increase of lysozyme in urine may not be due to proximal damage, and falsely positive reactions may occur in urinary tract infections (BERNARD and LAUWERYS, 1991).

#### **4.2.10 Tamm-Horsfall protein**

This nearly water-insoluble glycoprotein is secreted under normal conditions by the distal tubular system and is the major constituent of hyaline urinary casts. It has nephroprotective functions and probably plays a role in the immune defence against microorganisms (BOEGE, 1998). Tamm-Horsfall-glycoprotein (THG) or uromucoid is the most abundant protein of renal origin in normal urine (BERNARD and LAUWERYS, 1991). A high excretion in urine indicates a normal function of the distal tubulus, whereas a decrease suggests damage of the transport system mainly at Henle's loop and at the distal convoluted tubules and an increased calciuria (HÖRL, 1994; HOTZ, 1990).

#### **4.2.11 E-selectin in serum**

E-selectin in serum is a marker of endothelial cell activation. It belongs to a family of three adhesion molecules which facilitate the initial contact between leucocytes and vascular endothelial cells. Dependent on activation by cytokines, E-selectin is expressed on vascular endothelium (THOMAS, 1998g). Enzyme immunoassay kits for the determination of soluble E-selectin in serum are commercially available. In one study, in a control group of 108 healthy males (mean age 41.6 years), a 97.5 % cut-off value of about 75 µg/l was determined (STEVENSON et al., 1995).

#### **4.2.12 Laminin and anti-laminin antibodies**

Laminin is a glycoprotein in glomerular and tubular basement membranes which is involved in the renal filtration process. The presence of breakdown products of laminin in serum is indicative of the turnover of basement membranes (STEVENSON et al., 1995; PRICE et al., 1994; 1999). Laminin itself is a large molecule, but fragments of the LP1 component with molecular weights of 45000 to 55000 are found in the urine of diabetic patients (PRICE et al., 1999). The assay of the LP1 fragment in serum has been used in the clinical monitoring of patients with malignancies and liver disease (PRICE et al., 1994).

Basement membranes are known to play an important role in renal disease. Such diseases may arise from a modification in the rate of synthesis or a change in the structure/composition of certain of the components found in the basement membrane. Markers of basement membrane metabolism may have a role in identifying pathological change in the glomerular basement membrane and as such may act as indicators of glomerular dysfunction. Increases in LP1 fragment in serum and urine were observed in groups of diabetics (PRICE et al., 1994; 1995)

Anti-laminin antibodies may appear in Goodpasture syndrome and other immunological disorders (STEVENSON et al., 1995).

#### **4.2.13 Anti-glomerular basement membrane antibodies**

Circulating anti-glomerular basal membrane antibodies (AGBM) are detectable in cases of rapidly progressive glomerulonephritis as well as in Goodpasture's syndrome. The antibodies are directed against the C-terminal globular domain NC1 on the  $\alpha_3$  chain of type IV collagen which is an important structural component of all basement membranes (HÖRL, 1994; THOMAS, 1998a).

## 5 Case reports – results and discussion

The first case reports which described a temporal association between solvent exposure and renal disease were published more than hundred years ago. In these early reports, renal damage was described following acute inhalative or dermal exposure to turpentine (RHEINHARD, 1887; GLAESER, 1892; RIDDER, 1923).

Since then, a number of case reports have been published, the results of which have been repeatedly summarized in several reviews (VAN OETTINGEN, 1937; REIDENBERG et al., 1964; EHRENREICH, 1977; KLUWE, 1981; LAUWERYS et al., 1985; NELSON et al., 1990; PEDEREN, 1987; PHILLIPS et al., 1988; ROY et al., 1991; HOTZ, 1994).

Broadly, the effects reported may be classified according to the site of damage, i.e., tubular or glomerular (especially glomerulonephritis). Additionally, classification may be made according to acute or chronic development of the disease. Although it doesn't always follow, it generally can be said that tubular damage is described after acute exposure, while in case of glomerular diseases the temporal association is more variable.

Although this report addresses primarily the association of chronic solvents exposure with nephropathies, a brief cursory overview of case reports describing acute effects will be presented to illustrate the nephrotoxic potential of some individual solvents.

### Acute renal failure

In summary, the case reports show that, besides the well-known nephrotoxic haloalkanes (esp. tetrachloromethane), glycols, and toluene, exposure to other solvents of various chemical structure also may be linked to acute renal failure with tubular necrosis. The tubular lesion occurs rapidly, usually within few days after exposure, and therefore a relationship between exposure and effect is easily recognizable.

Acute tubular necrosis following oral ingestion or inhalation of tetrachloromethane has long been recognized and described in a number of case reports (for summary, see KLUWE, 1981). From the clinical cases described, it appears that the well-known hepatotoxic effect of tetrachloromethane is more apparent after oral ingestion, while kidney injury is more pronounced following inhalation. However, since the occupational use of tetrachloromethane is very restricted, intoxications with this compound are nowadays very unlikely. Exposure to other haloalkanes, i.e. trichloromethane (VAN OETTINGEN, 1937), dichloromethane (MILLER et al., 1985); 1,2-dichloroethane (YODAIKEN and BABCOCK, 1973); 1,2-dibromoethane (OLMSTEAD and FLEMINGTON, 1960, and 1,2-dichloropropane (POZZI et al., 1985; DI NUCCI et al., 1988), has also been linked in a few cases to acute tubular damage after short-term exposure (Tab. 5.1).

Other well-known nephrotoxicants that have caused numerous cases of intoxication are ethylene glycol and diethylene glycol (LAKIND et al., 1999). E.g., FRIEDMAN et al. (1962) give a detailed account of several cases of ethylene glycol poisoning following inadvertent ingestion and summarize several older reports. Diethylene

glycol has been recognized some decades ago as a cause of severe and even lethal renal failure after ingestion as solvent in drug application ("elixir of Sulfonamide Massengill") (CALVERY and KLUMPP, 1939; GEILING and CANNON, 1938). Lethal renal failure also occurred after high occupational exposure to the chemically related dioxane (JOHNSTONE, 1959). Rare cases of renal failure following ingestion of ethylene glycol monomethyl ether, neat (NITTER-HAUGE, 1970) or in combination with ethylene glycol (AUZEPY et al., 1973), have also been described.

A number of case reports, mostly on sniffers, but also on painters, have been published where inhalation of toluene containing solvents was followed by tubulopathies which often recurred at renewed exposure. Tubular damage with varying degrees of aminoaciduria, glucosuria, hyperuricemia, acidosis, and lowered serum concentrations of potassium, calcium, and phosphate were described (BENNETT and FORMAN, 1980; BOSCH et al., 1988; EHRENREICH, 1977; FISHMAN and OSTER, 1979; FLANAGAN and IVES, 1994; LAUWERYS et al., 1985; MARJOT and MCLEOD, 1989; PATEL et al., 1986; TAHER et al., 1974). Since the effects on the kidney may be accompanied by myoglobinuria, they may be also secondary and not due to direct kidney toxicity (EHRENREICH, 1977; MARJOT and MCLEOD, 1989; WEDEEN, 1992).

While the acute renal toxicity of the aforementioned solvents is substantiated by a number of cases, there are only a few reports that indicate that short-term high-exposure to other solvents may occasionally result in acute tubular damage as well.

There is one case report in which impairment of renal function was observed after very high exposure to xylene (MORLEY et al., 1970), and the authors of this study report a further case where kidney damage had been suggested.

Exposure to petroleum distillates has been related to acute tubular necrosis. In one case, inhalation of C<sub>5</sub> – C<sub>13</sub> aliphatic hydrocarbons was followed by acute renal failure at two subsequent exposures (LANDRY and LANGLOIS, 1998). Three other cases occurred after respiratory or dermal exposure to diesel oil (REIDENBERG et al., 1964; BARRIENTOS et al., 1977; CRISP et al., 1979) and a fourth case after oral ingestion of refined petrol (JANSSEN et al., 1988). In view of the widespread use of petroleum products, the scarcity of reports of acute renal failure is notable.

Similarly, despite its previously widespread use as degreasing solvent in industry and in dry-cleaning, trichloroethene has only sporadically been associated with acute renal failure (BRÜNING et al., 1998; GUTCH et al., 1965; DAVID et al., 1989). A few cases of hepatorenal toxicity from sniffing spot removers containing trichloroethene and other solvents have also been described (CLEARFIELD, 1970). In case of the related tetrachloroethene, transient albuminuria and red blood cells in urine were found after short-term high exposure of fireworkers (SALAND, 1967).

In the literature, the study of Narvarte et al. (1989) is often referred to as an example of a rare case of solvent intoxication with acute tubular damage progressing to chronic tubulointerstitial damage. The patient was exposed to mineral spirits and fuels. However, he suffered from ulcerative colitis and was therefore treated with sulfasalazine, a prodrug which is metabolized to 5-aminosalicylic acid (5-ASA). Growing evidence from a number of recent publications (summarized by ELSEVIERS

and DE BROE, 1998) has linked 5-ASA-treatment of inflammatory bowel disease to chronic tubulointerstitial nephritis. Therefore, the case described by NARVARTE et al. (1989) does not allow to draw any conclusion with respect to solvent-induced renal damage.

In the majority of the cases described in the literature, acute intoxication followed oral ingestion of large amounts of liquid or massive inhalative exposure in solvent abuse ("sniffing") or several hours of excessive occupational exposure without protection in badly ventilated small rooms. Therefore, although these cases demonstrate the nephrotoxic potential of acute high exposure, they may be of little relevance with respect to the nephrotoxicity of a long-term low exposure under conditions at today's workplaces.

**Tab. 5.1** Acute tubular toxicity of solvents – examples of case reports<sup>a</sup>

| Renal diagnosis*  | Patient<br>(sex, age) | Exposure<br>(history, route, condition)  | Agents   | Remarks  | Reference                 |
|---|-----------------------|--|--|--|---------------------------|
| Acute tubular necrosis  | M, 28 a               | Acute, oral,<br>accidental drinking  | Stain remover (1,2-dichloropropane)  |  | POZZI et al.<br>(1985)    |
| Acute tubular necrosis  | F, 20 a               | Acute, inhalative<br>sniffing  | Stain remover ( 98 % 1,2-dichloro-<br>propane, remaining trichloroethene,<br>dichloroethane)       |  |                           |
| Acute kidney failure  | M, 71 a               | Acute, oral,<br>suicide attempt  | Dry cleaning product<br>(90 % 1,2-dichloropropane,<br>10 % 1,1,1-trichloroethylene? <sup>b</sup> ) | Renal failure may have<br>been secondary to fatal<br>liver failure       | DI NUCCI et al.<br>(1988) |
| Acute renal failure   | M, 41 a               | Acute, inhalative + dermal,<br>occupational, floor tiling                            | Trichloroethene  |  | GUTCH et al.<br>(1965)    |
| Acute tubular necrosis<br>secondary to allergic<br>interstitial nephritis | M, 34 a               | Acute, inhalative,<br>occupational, computer ribbon<br>cleaning                      | Trichloroethene  | 8 h concentration probably<br>> 166 but < 3700 ppm                       | DAVID et al.<br>(1989)    |
| Acute tubular damage  | M, 17 a               | Acute, oral<br>suicide attempt   | Trichloroethene (70 ml)  |  | BRÜNING et al.<br>(1998)  |
| Transient albuminuria   | not<br>reported       | Acute (3 min), inhalative, occupa-<br>tional, closing leakage of drain pipe          | Tetrachloroethene  | Another exposed showed<br>RBC in urine, no renal<br>symptoms in 7 others | SALAND<br>(1967)          |
| Impairment of renal<br>function   | M, not<br>reported    | Acute (1 d), inhalative,<br>occupational, painting in small, ill-<br>ventilated room | Xylene (ca. 10000 ppm)   | Liver damage in this and a<br>further man, exitus in a<br>third          | MORLEY et al.<br>(1970)   |

| Renal diagnosis*  | Patient (sex, age) | Exposure (history, route, condition)  | Agents  | Remarks  | Reference                  |
|---|--------------------|---|---|--|----------------------------|
| Acute tubular necrosis  | M, 43 a            | Acute, inhalative + dermal, occupational, oil pits and motor piece cleaning | Petroleum naphtha (99 % C <sub>5</sub> to C <sub>13</sub> aliphatic hydrocarbons) | Recurrence of symptoms after reexposure                              | LANDRY and LANGLOIS (1998) |
| Acute tubular necrosis  | M, 33 a            | Acute (10 d), inhalative, occupational, exposure in lorry cab               | Diesel  |  | REIDENBERG et al. (1964)   |
| Acute tubular necrosis  | M, 28 a            | Acute, dermal, application as shampoo                                       | Diesel  | Effects after one application  | BARRIENTOS et al. (1977)   |
| Acute tubular necrosis  | M, 47 a            | Acute (several weeks), dermal, cleaning hands and arms after work           | Diesel  |  | CRISP et al. (1979)        |
| Acute tubular necrosis  | M, 23 a            | Acute, oral   | Refined petrol (600 ml)   |  | JANSSEN et al. (1988)      |
| Acute tubular damage progressing to chronic tubulointerstitial damage | M, 30 a            | Chronic (> 1a), inhalative + dermal, occupational helicopter maintenance    | Mineral spirits, helicopter fuel  | Patient suffered from ulcerative colitis, treated with sulfasalazine | NARVARTE et al. (1989)     |

\*: as given in the corresponding reference

a: Note: In the table, selected cases are reported to illustrate the acute nephrotoxic potential of individual solvents. No attempt was made to cover the entire number of cases described in the literature. Acute renal failure with tubular damage has been described in a great number of reports following short-term heavy exposure to tetrachloromethane, glycols (ethylene glycol, diethylene glycol), and toluene. These well-known renal toxins were not included in this table.

b: reported in original reference; however, this compound does not exist, and it cannot be decided if trichloroethylene or 1,1,1-trichloroethane was meant.



**Tab. 5.2** Glomerular damage and solvent exposure – case reports

| Renal diagnosis*       | Patient (sex, age) | Exposure (history, route, condition)  | Agents*   | Remarks  | Reference                                |
|------------------------|--------------------|---|---|--|--|
| Goodpasture's syndrome | M, 32 a            | 4 months, inhalative, occupational, lift truck operator at paint stripping tank | Paints, degreasing solvents                                 |  | BEIRNE and BRENNAN (1972); BEIRNE (1972) |
| Goodpasture's syndrome | M, 22 a            | 1 a, inhalative + dermal, occupational metal cleaning                           | Degreasing solvents   |  |  |
| Goodpasture's syndrome | M, 19 a            | 1 a, inhalative, occupational metal cleaning                                    | Degreasing solvents   |  |  |
| Goodpasture's syndrome | F, 28 a            | Chronic, inhalative, occupational, beautician                                   | Hair sprays, non-occupational: paint strippers and solvents |  |  |
| Goodpasture's syndrome | M, 21 a            | 3 a, inhalative, occupational, military service technician                      | Jet propulsion fuel   |  |  |
| RPGN                   | M, 44 a            | Chronic (20 a), inhalative, occupational house and sign painting                | Paint solvents and sprays                                   |  |  |
| Goodpasture's syndrome | F, 18 a            | Acute (2 weeks), inhalative, occupational gasoline selling                      | Hydrocarbon fumes   | Patients were identical twins, both cases occurring within 6 weeks | D'APICE et al. (1978)                    |
| Goodpasture's syndrome | F, 18 a            | Acute (5 d), inhalative, occupational spraying of ball-bearings                 | Mineral turpentine (white spirit)                           |  |  |
| Goodpasture's syndrome | F, 17 a            | Acute, inhalative, glue sniffing  | Glue (no details reported)                                  | onset of symptoms 3 weeks after exposure                           | ROBERT et al. (1988)                     |

| Renal diagnosis*       | Patient (sex, age) | Exposure (history, route, condition)                                      | Agents*  | Remarks   | Reference                   |
|------------------------|--------------------|---|--|---|-----------------------------|
| Goodpasture's syndrome | F, 19 a            | 2 months, inhalative + dermal?, occupational and spare time, hairdressing | Hair spray, permanent waving agents containing thioglycolic acid                       | Remission after withdrawal of waving agents                                     | BERNIS et al. (1985)        |
| Goodpasture's syndrome | M, 28 a            | 7 months, inhalative, occupational, car repair and servicing              | Solvent degreasers, petroleum distillates, benzene, dichloromethane, car exhaust fumes |   | BOMBASSEI and KAPLAN (1992) |
| Goodpasture's syndrome | M, 43 a            | One evening; inhalative, furniture cleaning at home                       | Tetrachloromethane   | Remission   | CARLIER et al. (1980)       |
| Goodpasture's syndrome | M, 22 a            | No data, car washer   | No data  | Exposure to petrol fumes mentioned by authors, but no data presented            | HEALE et al. (1969)         |
| Goodpasture's syndrome | F, 23 a            | 14 d, inhalative, home painting   | Hydrocarbon solvents   | Smoker; fatal relapse 6 w after reexposure                                      | KELLER and NEKARDA (1985)   |
| Goodpasture's syndrome | F, 16 a            | 10 months, inhalative, occupational, printing department                  | Dichloromethane, 1,1,1-trichloroethane   | Exacerbation after inhaling insect spray  | KEOGH et al. (1984)         |
| Goodpasture's syndrome | M, 26 a            | Acute, inhalative, occupational, spray painting                           | Paint thinner on petrol basis  | Excessive exposure (working without mask in non-ventilated room), fatal outcome | KLAVIS and DROMMER (1970)   |

| Renal diagnosis*                                  | Patient (sex, age) | Exposure (history, route, condition)                                      | Agents*  | Remarks                                      | Reference                                   |
|---|--------------------|---|--|--|---|
| Goodpasture's syndrome                            | F, 22 a            | Chronic?, inhalative, sniffing  | 1,1,1-trichloroethane  |  | NATHAN and TOSELAND (1979)                  |
| RPGN with anti-GBM antibodies                     | F, 22 a            | Acute, inhalative, domestic use of sprays                                 | Butane, ethylene oxide, nonyl-phenol, carboxy methyl cellulose, NaOH | Patient suffered from Hodgkin's disease      | KLEINKNECHT et al. (1980)                   |
| RPGN with anti-GBM antibodies                     | F, 17 a            | 3 a, inhalative, occupational hair dressing                               | Organic solvent vapors (reported similar to case above)              |  |   |
| Subacute proliferative GN with nephrotic syndrome | M, 59 a            | Acute, inhalative, occupational floor painting                            | Diacetone alcohol, ethanol   | Onset of symptoms ca. 4 weeks after exposure | VAN SCHEELE et al. (1976)                   |
| Goodpasture's syndrome                            | F, 20 a            | Recent exposure, occupational dry cleaning                                | No data reported   |  | WHITWORTH et al. (1974)                     |
| RPGN with anti-GBM antibodies                     | F, 16 a            | 6 – 9 months; inhalative glue sniffing                                    | "Pattex" (n-hexane, toluene, ethyl acetate, petrol fraction)         | Smoker                                       | BONZEL et al. (1987)                        |
| RPGN with anti-GBM antibodies                     | M, 28 a            | 1 a, inhalative, dermal, occupational maintenance cleaning                | Stoddard solvent   |  | DANIELL et al. (1988)                       |
| Membranous GN                                     | M, 24 a            | Chronic (> 2 a); inhalative, dermal, occupational, film making laboratory | Many different solvents <sup>a</sup>                                 |  | EHRENREICH (1977); EHRENREICH et al. (1974) |

| Renal diagnosis*                      | Patient (sex, age) | Exposure (history, route, condition)                                  | Agents*  | Remarks  | Reference                                   |
|---------------------------------------|--------------------|---|--|--|---|
| Membranous GN                         | M, 45 a            | Chronic (18 a), inhalative, occupational moulding in plastic industry | Solvents, plastic fumes, formaldehyde                            |  | EHRENREICH (1977); EHRENREICH et al. (1974) |
| Membranous GN                         | M, 47 a            | Chronic (> 20 a), occupational, metal cleaning, fine mechanics        | Solvents (tetra-, trichloroethene, acetone, methyl ethyl ketone) | Nephrotic syndrome was detected 10 a before      |   |
| Membranous GN                         | M, 44 a            | Chronic (11 a), occupational, fine mechanic, metal assembly           | Solvents (tetra-, trichloroethene, acetone, methyl ethyl ketone) | Work associate of aforementioned case            |   |
| Membranous GN                         | M, 30 a            | 2 months, 8 h/d likely occupational                                   | Paint thinner, petrol  | Father and daughter, daughter fell ill 8 a later | RAVNSKOV (1979)                             |
| Acute poststreptococcal GN            | F, 10 a            | Few days, no further data   | Paint thinner  |  |   |
| Membranous GN with nephrotic syndrome | M, 59 a            | > 27 months, occupational, no further data                            | Hydrocarbons (no further data)                                   | Recurrence of symptoms at several re-exposures   | CAGNOLI et al. (1980)                       |
| IgA-glomerulonephritis                | M, 28 a            | Chronic (9.5 a), inhalative, occupational plumber work                | Tetrahydrofuran  |  | ALBRECHT et al. (1987)                      |
| Focal segmental glomerulosclerosis    | M, 60 a            | Chronic (40 a), inhalative, occupational bag manufacturing            | Toluene  | Patient also suffered from myelofibrosis         | BOSCH et al. (1988)                         |

\*: as given in the corresponding reference

a: patient reported exposure to acetone, methyl ethyl ketone, butyl acetate, butyl alcohol, isopropyl alcohol, methyl alcohol, tetrahydrofurane, tetrachloromethane, chloroform, dichloromethane, dichloroethane, trichloroethene, cyclohexane, toluene, xylene, dimethylformamide, and acetonitrile.

## Glomerulonephritis

Most case reports which describe associations of solvent exposure and glomerular damage (Tab. 5.2) refer to cases suffering from Goodpasture's syndrome or rapidly progressive glomerulonephritis (RPGN) with anti-GBM antibodies (HEALE et al., 1969; KLAVIS and DROMMER, 1970; BEIRNE, 1972; BEIRNE and BRENNAN, 1972; WHITWORTH et al., 1974; VAN SCHEELE et al., 1976; D'APICE et al., 1978; NATHAN and TOSELAND, 1979; KLEINKNECHT et al., 1980; KEOGH et al., 1984; KELLER et al., 1985; BERNIS et al., 1985; BONZEL et al., 1987; ROBERT et al., 1988; DANIELL et al., 1988; BOMBASSEI and KAPLAN, 1992). Although it is often stated in the literature that this association is most frequently observed in young men, the data from Tab. 5.2 reveal that both sexes are similarly affected. A few cases of membranous GN (EHRENREICH, 1977; EHRENREICH et al., 1974; CAGNOLI et al., 1980) and one case of IgA-nephropathy (ALBRECHT et al., 1987) have also been associated with solvent exposure.

In view of the extreme rareness of Goodpasture's syndrome (KELLER and NEKARDA, 1985), both with respect to the absolute number of such cases annually and the relative frequency compared to other types of GN (see Tab. 2.1), it is noteworthy how often this disease or courses of illness which are consistent with it have been described in case reports. It is conceivable that the special interest in this severe and uncommon disease may have led to a considerable publication bias.

The assessment and evaluation of case reports with respect to an association between chronic solvent exposure and glomerulonephritis is hampered by the difficulty to demonstrate that the temporal relationship between exposure and outbreak of disease is causal and not coincidental and by the insufficient description of exposure.

HOTZ (1994) points out that Goodpasture's syndrome may relapse and patients may have had episodes of pulmonary hemorrhages long before their presentation with Goodpasture's syndrome, but their renal function or the presence of anti-GBM antibodies was unknown at the earlier episodes. This would suggest that the disease may have already been present but not recognized before the solvent exposure.

Exposure is often not described in much detail in the case reports. Named solvents include most of the substances or mixtures that are widely used, for example, tetrahydrofurane (ALBRECHT et al., 1987), toluene (BOSCH et al., 1988), Stoddard solvent (DANIELL et al., 1988), mineral turpentine (white spirit) (D'APICE et al., 1978), haloalkenes and ketones (EHRENREICH et al., 1974, EHRENREICH, 1977), and haloalkanes (KEOGH et al., 1984; NATHAN and TOSELAND, 1979) including tetrachloromethane (CARLIER et al., 1980). In other reports, only broad groups of agents such as paints, thinners, degreasing solvents, or glues are mentioned (BEIRNE and BRENNAN, 1972; BEIRNE, 1972; RAVNSKOV, 1979a; BERNIS et al., 1985; ROBERT et al., 1988). Generally, no data with respect to the presence of other possible nephrotoxic agents (e.g. heavy metals) are presented. However, BERNIS et al. (1985) reported that remission of symptoms occurred not after avoidance of the solvents initially suspected but after withdrawal of a waving agent which was used at the same occupation.

Information on exposure is lacking in some reports (HEALE et al., 1969; CAGNOLI et al., 1980; WHITWORTH et al., 1974). The composition of the solvent mixture reported by KLEINKNECHT et al. (1980) is probably not correct since it seems impossible that ethylene oxide, a carcinogenic gas, would have been used in domestic sprays. Moreover, it was reported that this alkali-labile compound occurred in combination with sodium hydroxide.

Finally, exposure to solvents is widespread while glomerulonephritis is rare, and case reports are not suitable to distinguish between mere coincidence or causal relationship. Therefore, case reports can only be used as a starting point for more convincing epidemiological studies.

## 6 Epidemiological studies – results and discussion

### 6.1 Cohort studies and other longitudinal studies

Numerous retrospective cohort mortality studies are available on workers in various solvent-related industries. Their main focus usually was the occurrence of cancer, but non-cancer effects were reported as well. There are no cohort studies on morbidity from renal diseases, though a few longitudinal studies have been carried out in groups of solvent-exposed active workers and some follow-up studies have been published on patients suffering from glomerulonephritis (see end of this chapter)

The studies have been reviewed or summarized by DELZELL et al. (1988); PHILLIPS et al. (1988); and HOTZ (1994). Moreover, a meta-analysis of overall 55 mortality studies of workers exposed to organic solvents has been carried out by CHEN and SEATON (1996), including 12 studies in which data for "genitourinary system" disease as cause of death were reported. A brief summary of the findings from the studies is presented in Tab. 6.1. The meta-analysis of CHEN and SEATON (1996) contains no information on the publications of KAPLAN (1986), HANIS et al. (1985), DIVINE et al. (1985), DAGG et al. (1992), PARK et al. (1990), and WONG (1990). None of the studies showed a statistically significant excess risk of death from "genitourinary diseases" or "nephritis and nephrosis". Instead, risks in general were lower; this is likely to be explained by the "healthy worker effect" which is frequently seen in occupational cohorts (KREIENBROCK and SCHACH, 1997).

An evaluation of the study results has to deal with several difficulties.

Firstly, the studies reported mortality for the broad diagnostic categories "genitourinary diseases" or "nephritis and nephrosis". Glomerulonephritis – which may be associated with solvent exposure according to the results from the case reports and the case control studies – presently accounts for about one third of basically lethal ESRD<sup>1</sup>. Some other non-neoplastic renal diseases are a primary cause of death as well. Thus, probably increased incidences of glomerulonephritides may be concealed by other kidney diseases and causes of disease.

Secondly, even if it is assumed that these diagnostic categories would exclusively contain fatal cases of ESRD due to GN, the low incidence of death from renal or genitourinary disease represents a further problem: Although some of the cohorts were comprised of considerably more than 10000 workers, the numbers of deaths from renal or genitourinary disease were rather low. For example KAPLAN (1986) reports in his cohort of 19991 workers 33 cases of genitourinary diseases, 13 of these were nephritis and nephrosis. As a consequence the power of the available studies to detect kidney diseases is rather low. This has been illustrated by the

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<sup>1</sup> Note: strictly speaking, by definition life-saving therapy is applied in case of ESRD (see 2.2.1, page 19), and such patients may die from other diseases unrelated to renal damage.

following calculation made by CHURCHILL et al. (1983): Using ESRD due to glomerulonephritis (GN) as outcome, assuming an incidence of ESRD of 90 p.m.p. (patients per million population) per year and that 30 % of ESRD are caused by GN, the number of patients with ESRD due to GN is 30 p.m.p. per year<sup>2</sup>. The probability of an individual developing ESRD from GN is therefore 0.00003. If solvent exposure increased this risk ten times, the sample size required (assuming a type I error of 5 %, a type II error of 20 %, and a one-tailed test of significance) would be 22 000/group. Apart from the meta-analysis (CHEN and SEATON, 1996), only four studies nearly reached or exceeded this sample size (BOICE et al., 1999; RUSHTON and ALDERSON, 1981, and RUSHTON, 1993a; RUSHTON and ALDERSON, 1983, and RUSHTON, 1993b; HANIS et al., 1985).

Thirdly, glomerulonephritis often develops slowly over the course of many years or even decades and may be unrecognized during that time. Even after the disease is diagnosed, it may take many years until terminal renal failure develops and the stage of ESRD requiring dialysis or transplantation is reached. During this long period, the patient may have died from another non-GN related disease which will then be noted as the cause of death in a mortality study. Also, glomerulonephritis may progress to glomerulosclerosis. Glomerulosclerosis is a common result of different diseases, and the primary underlying disease is no longer detectable when this stage is reached (BALDAMUS and POLLOK, 1994; REMUZZI and BERTANI, 1990). Besides glomerulonephritis, hypertension is an important risk factor for the development of glomerulosclerosis and vice versa (HEIDLAND and HEIDBREder, 1994). This means that in such cases the cause of death could have been misclassified as hypertension, while the initial glomerulonephritis would have been unrecognized. As a consequence mortality studies are not useful for the investigation of diseases which have a low rate of fatality, which is true in case of glomerulonephritis (or other types of chronic nephropathy).

A fourth point concerns exposure assessment. In many of the cohort studies, exposure estimates were based on job titles. However, according to HOTZ (1994), it is difficult to conclude from working in an industry branch in which solvents are used to actually being exposed to solvents. This uncertainty will lower the study power, and effects of mortality that may occur among highly exposed subcohorts may be diluted by the larger proportion of lower exposed workers.

In summary, retrospective cohort mortality studies are not adequate to reveal relationships between solvent exposure and chronic renal diseases.

### **Follow-up studies on patients with glomerulonephritis**

Some follow-up studies have been published on patients suffering from glomerulonephritis. These studies were aimed at the question if a discontinuation of exposure might have a beneficial effect on the progression of disease (RAVNSKOV, 1979; 1986; YAQOOB et al., 1993). Since these observations were made in the

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<sup>2</sup> These assumptions are a little lower, but reasonably agree with the actual incidences of ESRD and GN reported for Germany (see 2.2.2 and 2.3.3).



context of case-control studies, they have been described and evaluated together with these studies in chapter 6.2.

### **Occupational studies on active workers**

A few longitudinal studies have been carried out in groups of active workers at solvent-exposed workplaces (BROUWER et al., 1991; OSTERLOH and FELDMAN, 1993; ROCSKAY et al., 1993; STENGEL, 1998; GERIN et al., 1997). In these studies, biomarkers of renal alterations such as albumin and NAG-excretion were monitored. Some of these studies also were cross-sectional (ROCSKAY et al., 1993; STENGEL, 1998), and the parameters measured as biomarkers of renal alterations were the same as those generally used in cross-sectional studies. Therefore, the results of those studies have been summarized and evaluated in the chapter on cross-sectional studies (see 6.3).

| Industry/agent                                      | Cohort   |       | Diagnostic category     | No. of death observed in diagnostic category | SMR (95 % C.I.)    | Reference                   |
|---|--|-------|-------------------------|--|--------------------|-----------------------------|
|   | Definition   | Size  |                         |  |                    |                             |
| Paint and coatings manufacturing                    | > 1 a employed<br>1946 – 1980                        | 16243 | Genitourinary diseases  | 15 (all workers)                             | 57 (not reported)  | MORGAN et al. (1981)        |
|   |  |       |                         | 7 (solvent-exposed subgroup)                 | 61 (not reported)  |                             |
| Oil refinery  | > 1 a employed<br>1950 – 1975                        | 34708 | Nephritis and nephrosis | 36 (all workers)                             | 85 (not reported)  | RUSHTON and ALDERSON (1981) |
|   |  |       | Chronic nephritis       | 6 (subgroup, one refinery)                   | 152 (not reported) |                             |
|   | > 1 a employed<br>1950 – 1989<br>(further follow-up) | 34569 | Nephritis and nephrosis | 39   | 82 (not reported)  | RUSHTON (1993a)             |
| Oil distribution                                    | > 1 a employed<br>1950 – 1975                        | 23306 | Nephritis and nephrosis | 15   | 46 (not reported)  | RUSHTON and ALDERSON (1983) |
|   | > 1 a employed<br>1950 – 1989<br>(further follow-up) | 23306 | Nephritis and nephrosis | 21   | 53 (not reported)  | RUSHTON (1993b)             |
| Oil refinery  | > 1 a employed<br>1962 – 1976                        | 19991 | Genitourinary diseases  | 33   | 63 (not reported)  | KAPLAN (1986)               |
|   |  |       | Nephritis and nephrosis | 13   | 73 (not reported)  |                             |
| Exxon refineries and chemical plants                | > 1 a employed<br>not reported                       | 21698 | Genitourinary diseases  | 51   | 101 (n.s.)         | HANIS et al. (1985)         |
| Texaco refineries and chemical plants               | > 5 a employed<br>1947 – 1977                        | 19077 | Genitourinary diseases  | 43   | 53 (38 – 71)       | DIVINE et al. (1985)        |
| Chevron petroleum refinery                          | > 1 a employed<br>1950 – 1986                        | 14074 | Genitourinary diseases  | 36   | 62 (43 – 85)       | DAGG et al. (1992)          |
| Dry cleaning/ tetrachloro-ethene and other solvents | ≥ 1 a employed<br>1960 – 1982                        | 1690  | Genitourinary diseases  | 10   | 98 (47 – 180)      | BROWN and KAPLAN (1987)     |

**Tab. 6.1** Cohort mortality studies of solvent-exposed workers – summary of data for deaths from renal or genitourinary diseases.

| Industry/agent   | Cohort                           |       | Diagnostic category                             | No. of death observed in diagnostic category | SMR (95 % C.I.)    | Reference              |
|--|----------------------------------|-------|---|--|--------------------|------------------------|
|  | Definition                       | Size  |   |  |                    |                        |
| Dry cleaning/ tetrachloroethene and other solvents                         | ≥ 1 a employed<br>1948 – 1979    | 5790  | Chronic nephritis                               | 6  | 60 (20 – 120)      | BLAIR et al. (1990)    |
| Photographic film base manufacture/ dichloromethane                        | ≥ 1 a employed<br>1964 – 1988    | 1013  | Genitourinary diseases                          | 5  | 116 (n.s.)         | HEARNE et al. (1990)   |
| Aerospace industry/ hydrocarbons   | ≥ 10 a employed<br>1950 – 1986   | 583   | Chronic nephritis (only one subgroup evaluated) | 1  | 193 (5 – 1068)     | PARK et al. (1990)     |
| Reinforced plastics/ styrene   | ≥ 0.5 a employed<br>1948 – 1977  | 15908 | Genitourinary diseases                          | 7  | 129.6 (n.s.)       | WONG (1990)            |
| Aircraft maintenance/ trichloroethene, hydrocarbons                        | ≥ 1 a employed<br>1952 – 1982    | 14457 | Nephritis and nephrosis                         | 25   | 113 (73 – 167)     | SPIRTAS et al. (1991)  |
| Aircraft manufacturing/ tri-, tetrachloroethene, mixed solvents, chromates | ≥ 1 a employed<br>1960 – 1996    | 77965 | Nephritis and nephrosis                         | 137  | 97 (82 – 115)      | BOICE et al. (1999)    |
| FFMPC <sup>a</sup> / trichloroethene, cutting fluids, kerosene, other      | ≥ 0.25 a employed<br>1951 – 1989 | 3814  | Genitourinary diseases                          | 3  | 21 (4 – 63)        | RITZ (1999)            |
| Various (meta-analysis from data of 12 studies)                            | –                                | 70251 | Genitourinary diseases                          | Not reported                                 | 69.3 (53.0 – 90.7) | CHEN and SEATON (1996) |

n.s.: not significant

a: Fernald Feed Materials Production Center, Ohio, uranium extraction and production plant.

## 6.2 Case-control studies

### 6.2.1 Description of studies

The reports of cases of glomerulonephritides occurring in solvent-exposed patients (see chapter 5) prompted a number of case-control studies. These studies have been summarized or reviewed (CHURCHILL et al., 1983; DANIELL et al., 1988; PHILLIPS et al., 1988; HOTZ and BOILLAT, 1989; NELSON et al., 1990; ROY et al., 1991; TRIEBIG and BLUME, 1992; YAQOOB and BELL, 1994; DE BROE et al., 1996; ELSEVIERS and DE BROE, 1998; BRAUTBAR and BARNETT, 1999); most comprehensively by HOTZ (1994).

Overall, 24 case-control studies were identified in the literature. A further study has only briefly been mentioned by MULLIN et al. (1990). It was reported to have shown no association between hydrocarbon exposure and chronic glomerulonephritis, but it was not published and thus cannot be evaluated.

The cases covered in the 24 control-studies comprised mostly primary, non-acute glomerulonephritides with all stages of renal function from early renal failure to end-stage renal disease. In a few studies, the case group included patients with CRF (NUYTS et al., 1985) or ESRD of different origin (STEENLAND et al., 1990), various stages of diabetic nephropathy (YAQOOB et al., 1994b), or with GN related to systemic diseases (PAI et al., 1998). In most studies, diagnoses were verified and specified by renal biopsy (Tab. 6.1). Other occupational (NUYTS et al., 1995) or life-style factors (WAKAI et al., 1999) were additionally evaluated with respect to an association with the occurrence of GN.

Controls either came from the general population, usually matched by age, sex, and residential area (ASAL et al., HARRINGTON et al., 1989; NELSON et al., 1995; NUYTS et al., 1995; STEENLAND et al., 1990; WAKAI et al., 1999), were patients with other renal diseases such as polycystic kidneys, hypertensive nephrosclerosis, congenital anomalies, renal stones, chronic pyelonephritis or hyperuricaemia (FINN et al., 1980; FRANCHINI et al., 1982; LAGRUE, 1976; PORRO et al., 1992; RAVNSKOV, 1977, 1978, RAVNSKOV et al., 1979; ZIMMERMAN et al., 1975), or patients with non-renal diseases (BELL et al., 1985; FINN et al., 1980; FRANCHINI et al., 1982; PORRO et al., 1992; RAVNSKOV et al., 1979; SESSO et al., 1990; VAN DER LAAN, 1980, ZIMMERMAN et al., 1975). Several studies used two control groups (ZIMMERMAN et al., 1975; LAGRUE et al., 1977; RAVNSKOV et al., 1979; FINN et al., 1980; PORRO et al., 1992; YAQOOB et al., 1992).

Meta-analyses have been carried out by RAVNSKOV (2000a) (Fig. 6.1, Tab. 6.1) and TRIEBIG and BLUME (1992; see also GIERSIEPEN and STRAIF, 1992).

TRIEBIG and BLUME (1992) evaluated seven studies published up to 1989 (LAGRUE et al., 1977; RAVNSKOV, 1978; RAVNSKOV et al., 1979, 1983; FINN et al., 1980; VAN DER LAAN, 1980; HARRINGTON, 1989). From all of these seven studies, a significantly increased OR of 2.8 was calculated. For further calculations only those four studies fulfilling a catalogue of quality criteria were taken into account. Depending on the method used (no details reported), four OR ranging from 1.2 to 2.1 were calculated; and three of these four OR were statistically significant. Neither the

quality criteria were described by TRIEBIG and BLUME (1992), nor was mentioned which of the studies had fulfilled these criteria. Therefore, this analysis was not further taken into account.

The recently published meta-analysis of RAVNSKOV (2000a) evaluated all case-control studies published between 1975 and 1996 (summarized in Tab. 6.2). Four studies were excluded from the meta-analysis because no odds ratio could be calculated either due to the small number of participants (RAVNSKOV, 1978) or to study design (BELL et al., 1985; RAVNSKOV et al., 1983; HARRISON et al., 1986). The follow-up studies of YAQOOB et al. (1993, 1994a,b) were also not taken into account since in these studies groups of patients with different stages of diseases were compared. It must be noted that all of these studies which were excluded in the meta-analysis described a positive association between GN and exposure to solvents.

A general overview of the design and results of all case-control studies is given in Tab. 6.2.

In 19 of the 24 studies, a significantly increased odds ratio (OR) and/or a positive association between solvent exposure and glomerulonephritis has been found. Generally, the case groups consisted of patients with primary, non-systemic GN. However, an association between hydrocarbon exposure and diabetic nephropathy (YAQOOB et al., 1994) and with patients with GN due to systemic vasculitis (PAI et al., 1998) has also been observed.

Among the 24 studies, no significantly increased odds ratios were found in five studies (VAN DER LAAN, 1980; FRANCHINI et al., 1982; HARRINGTON et al., 1989; ASAL et al., 1996; WAKAI et al., 1999).

## **6.2.2 Analysis of factors influencing the results**

In the following, the basic results and factors which are important for the consideration of results are discussed.

### **6.2.2.1 Case definition**

#### **Type of disease**

Generally, the case groups consisted of patients that suffered from a number of different types of primary, non-systemic glomerulonephritides, and normally case groups were heterogeneous with respect to the type of GN included (Tab. 6.1). Diagnostic classification included biopsy verification in 100 % of GN-patients in the majority of the studies, but was 38 - 78 % in some, mostly earlier studies (ZIMMERMAN et al., 1975; LAGRUE et al., 1977; RAVNSKOV, 1978; FINN et al., 1980; ASAL et al., 1996). The study of STEENLAND et al. (1990) was not restricted to clinical cases of GN but resorted to a kidney registry which registers all new cases of ESRD irrespective of the underlying disease and including only 5 % of biopsied cases.

The use of heterogeneous case definitions may obscure an association between exposure and a specific type of GN. Moreover, a comparison of studies is hampered

when some types of GN are included in the case group of one study but are explicitly excluded or even put into the control group in another. E.g., patients with post-streptococcal GN were studied by RAVNSKOV (1978), whereas patients with a high anti-streptolysin titre or a streptococcal infection were excluded by BELL et al. (1985) or PORRO et al. (1992), respectively.

Another problem seems to be the inclusion of patients with IgA-nephropathy, since this type of glomerular disease has been assumed not to be related to solvent exposure. No significant association with hydrocarbon exposure and IgA-nephropathy was found by WAKAI et al. (1999), and the inclusion of such patients in the study of HARRINGTON et al. (1989) has been claimed to induce a selection bias (YAQOOB et al., 1992) which at least partially could account for the negative results of this study. Patients with IgA-nephropathy were excluded in the study of PAI et al. (1997). On the other hand, IgA-nephropathy was associated with hydrocarbon exposure in two other investigations (STENGEL et al., 1995, 1996; PORRO et al., 1992).

Patients with GN related to systemic disease or renal damage secondary to other diseases were generally excluded from the studies. However, one study on patients with GN due to systemic vasculitis indicated a possible association with solvent exposure (PAI et al., 1998), and in another study, an association between diabetic nephropathy and exposure to solvents (solvents not specified) was demonstrated (YAQOOB et al., 1994).

### **Genotype**

The role of human genotypic polymorphism of microsomal metabolism in a group of solvent-exposed patients (solvents not specified) suffering from different types of GN was compared to healthy controls (PAI et al., 1997) (Tab. 6.1). No significant differences in the genotypic frequencies of CYP2D6, GSTM1, GSTT1, and NAT-2 were determined in the GN group overall, but, compared to controls, in the subgroup of patients with membranous GN, a significant increase in GSTM1 *null* to *wild type* and in NAT fast to slow acetylators was observed. However, the number of patients investigated was small, and the relevance of these findings with respect to the development of GN in hydrocarbon exposed humans is not clear.

### **Severity of disease**

Comparison of the outcome of studies should consider that the status of renal function differs between the studies. Renal function as judged by serum creatinine concentration or GFR covered a wide range from early to advanced renal failure and to ESRD requiring dialysis, but was not always reported in detail.

The relationship between status of renal function and hydrocarbon exposure was specifically addressed in the meta-analysis of RAVNSKOV (2000a) (Tab. 6.1). For groups of patients suffering from acute or an early stage of glomerulonephritis<sup>3</sup>

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<sup>3</sup> Note: In the meta-analysis, it was possible in case of two studies (STENGEL et al., 1995, ASAL et al., 1996) to separate the patients for more detailed evaluation into two groups: one with normal function or/and mild renal impairment and one with more severe and chronic renal failure.

(HARRINGTON et al., 1989; ASAL et al., 1996; VAN DER LAAN, 1980; STENGEL et al., 1995), the combined mean weighted odds ratio was lowest and not significantly different from control (OR = 1.0) This meta-analysis does not include the more recent study of WAKAI et al. (1999), but their results (no increased OR in a group of IgA-patients with mostly non-reduced renal function) are consistent with those of the meta-analysis.

In the meta-analysis, significantly increased mean weighted odds ratios were observed for the groups of patients that suffered from chronic renal failure and for the groups with end-stage renal failure (RAVNSKOV, 2000a) (Fig. 6.1, Tab. 6.1). An individual study (ASAL et al., 1996) also observed a significantly increased odds ratio for the group of patients with a high serum creatinine level (which indicates impaired kidney function).

These results suggest that exposure to hydrocarbons may be associated with more advanced disease and inversely related to renal function.

### **"Follow-up" of patient groups with GN**

Consistent with this suggestion are follow-up studies in which it was observed that continued hydrocarbon exposure may be a risk factor in the progression of renal failure in glomerulonephritic patients (BELL et al., 1985b; YAQOOB et al., 1993a) and the findings of a study which specifically investigated workers with diabetic nephropathy. In this study, the hydrocarbon exposure estimates were higher in patients with more advanced than in those with less advanced diabetic nephropathy (YAQOOB et al., 1994b).

In a short notice, RAVNSKOV and FORSBERG (1979) mentioned that the mean GFR increased during follow-up in a group of GN-patients that were exposed to solvents before, but not during follow-up. In contrast, GFR further deteriorated in a second group of patients with chronic GN that had never been exposed to solvents and in a third that had been exposed before and during follow-up. No details were reported, and the main paper was never published because of indiscrepancies detected in it by BENGTTSSON (1985). A paper of the same main author which was published shortly afterwards on the same topic (RAVNSKOV, 1986) also described that patients with a subnormal GFR who discontinued exposure had a more favorable course than those who were further exposed. However, this study has some weaknesses and should be viewed with caution because of the quarrel with BENGTTSSON (1985) (see above). We feel that both reports should only be seen as initiators that prompted further follow-up studies.

BELL et al. (1985b) reported that in nine of 26 patients with proliferative GN and continued heavy occupational solvent exposure, renal failure had progressed to ESRD after a mean follow-up of 83 months. No such progression was seen after a mean of 92 months in another group of 24 patients with proliferative GN but with moderate to low exposure.

A more detailed study was performed by YAQOOB et al. (1993a) (Tab. 6.2) who investigated the role of hydrocarbon exposure in the progression of renal failure in two groups of patients. At the beginning of a 5 year follow-up period, patients in group one, but not in group two, showed progressive renal failure (PRF). Hydro-

carbon exposure scores during follow-up were significantly higher in the group with PRF, and in this group, 73 % of patients continued to be exposed to hydrocarbons, compared to 13 % in the group without PRF. At the time of renal biopsy, serum creatinine was higher in group 1 but the degree of proteinuria and hypertension were similar. During follow-up, the course of disease was much less favorable in group 1 (rise in serum creatinine and of the proportion of hypertensive and of ESRD patients) than in group 2 (no rise in serum creatinine, decline in proteinuria, five patients who discontinued exposure showed improvement in renal function). Indicators of tubular damage (NAG, LAP, RBP) also were higher in group 1. These results suggest that continued hydrocarbon exposure may play a role in the progression of renal failure. However, the evaluation is hampered by some weaknesses in the study: Both groups were only of limited comparability at the beginning, and many results and comparisons are only reported on a group basis. Also, it is not clear if the patients which developed ESRD were those who were exposed (or to what extent they were exposed) during follow-up. Moreover, the use of creatinine measurements in the progression of renal failure has been criticized because it may yield inaccurate estimates with respect to the development of the disease (WALSER et al., 1988). Finally, YAQOOB et al. (1993a) give no data on therapy, so that it cannot be judged if or to what extent different medical treatment could have contributed to the differences in the course of disease between both groups.

ASAL et al. (1996) found high exposure scores within the group of controls in their study. The authors discussed whether persons in this control group who had very high exposure scores may develop loss of renal function that has not yet reached a stage – but may so in the future – where symptoms begin to be obvious enough for these persons to attract medical attention. ASAL et al. (1996) suggested that a follow-up on this controls may be carried out, but – to our knowledge – no such study has been published to date.

### **Drop-out due to death**

The meta-analysis of RAVNSKOV (2000a) further points to another bias not discussed previously which may be induced by drop-out due to death ("survival bias"). If renal failure is associated with hydrocarbon exposure, the death of patients selected for the study prior to the interview may lead to an underestimation of exposure in the case group because end-stage renal failure is the most usual cause of premature death in GN-patients. Therefore, in the meta-analysis, mean weighted odds ratios were calculated separately for studies with 1 % or less drop-outs only and for all studies including those with  $\geq 5$  % or more drop-outs (RAVNSKOV et al., 1979; FRANCHINI et al., 1982; STEENLAND et al., 1990; NUYTS et al., 1995; ASAL et al., 1996). The results indicate that the mean-weighted odds ratio increase when studies with a higher drop-out due to death are excluded from the analysis (Tab. 6.1).



**Tab. 6.1** Weighted mean odds ratios (OR) for hydrocarbon exposure for patient groups with different renal functional status. OR were calculated separately for study groups with more and with less than 1 % drop-out due to death. Further explanation is given in the text. Data from meta-analysis (RAVNSKOV, 2000a).

| Renal functional status of patients | Odds ratio, weighted mean (95 % confidence interval)<br>(no. of groups) |  |
|-------------------------------------|---|--|
|                                     | Including groups with > 1 % drop-outs due to death                      | Excluding groups with > 1 % drop-outs due to death |
| All studies combined                | <b>1.6*</b> (1.2 – 2.0)   | <b>3.7*</b> (2.9 – 4.6)                            |
| All categories of renal function    | <b>3.1*</b> (2.3 – 4.3)<br>(n=4)  | <b>3.1*</b> (2.2 – 4.5)<br>(n=2)                   |
| Acute or early chronic GN           | 1.0 (0.7 – 1.4)<br>(n=4)  | 0.95 (0.6 – 1.4)<br>(n=2)                          |
| CRF                                 | <b>2.2*</b> (1.5 – 3.2)<br>(n=4)  | <b>3.1*</b> (1.5 – 6.2)<br>(n=2)                   |
| ESRD                                | <b>2.2*</b> (1.6 – 2.8)<br>(n=4)  | <b>5.9*</b> (3.8 – 9.3)<br>(n=3)                   |

\* Bold values indicate statistically significant mean weighted OR.

#### 6.2.2.2 Exposure assessment

Exposure to solvents or hydrocarbons in general (including fuels etc.) was assessed by means of questionnaires and/or interviews. Exposure was categorized on a dichotomous scale (exposed/non-exposed) or, in most studies, some graded exposure score was calculated considering at least duration and/or frequency, and sometimes intensity of solvent exposure. In the studies of ZIMMERMAN et al. (1978), LAGRUE et al. (1976, 1977), and HARRISON (1986), exposure estimates were not hydrocarbon specific but included heavy metals and were poorly defined.

In only one study, estimated numeric values of lifetime hydrocarbon exposure were given (ASAL et al., 1996; NELSON et al., 1995). However, many studies used a semi-quantitative exposure scoring system originally developed by RAVNSKOV et al. (1979) and BELL et al. (1985) or modifications of this system. Duration, frequency, and intensity of exposure to organic solvents and fuel hydrocarbons in occupational and non-occupational (spare-time) activities is assessed by questionnaire, the score is then calculated as the product of person's estimate of exposure per month (or weeks), the number of months the activity had been practised, and the appropriate intensity factor (Tab. 6.1). In case of more than one activity with exposure, all individual scores are summarized. A connection between this retrospective score and some biomarkers of renal effects in a working population has been described in a cross-sectional study (HOTZ et al., 1989). In the study of HARRINGTON (1989), a different exposure scoring system was used with a logarithmic weighting scale for intensity (score of zero, 1, 10, or 100) and exposure indices calculated by multiplying

this factor with duration (expressed as full years) of exposure. It must be mentioned that HOTZ (1994) suggested that this system may lead to high scores which are in conflict to reasonable exposure estimates.

An exposure-response-relationship was apparent in several studies in which odds ratios were higher at higher scores of occupational exposure, and in studies in which the risks were only significantly increased in occupationally, but not in non-occupationally (less) exposed groups (RAVNSKOV et al., 1979, 1983; PORRO et al., 1992; STENGEL et al., 1995, 1996). No significantly increased risk was observed by VAN DER LAAN (1980) in a group of patients with rather low exposure. This study used a scoring system similar to RAVNSKOV et al. (1979). The findings from these studies suggest that a significant association can only be observed after exposure has exceeded a certain level.

If the scoring system reveals only slight or no differences in exposure between cases and control groups, the validity of a study with respect to an association between solvent exposure and renal disease will be lowered. Such an effect is likely to play a role in the study of HARRINGTON et al. (1989). Even though the individual exposure could have been overestimated (see above), only 9 out of 50 cases in this study were classified as exposed (score > 99). Low exposure estimates for cases were also described by VAN DER LAAN (1990), while ASAL et al. (1996) found that the exposure scores in the control group were rather high and similar to the exposed group. In all of these three studies, the difference in exposure may have been too low to reveal an association between exposure and disease. A relationship between exposure to special groups of solvents or fuels and disease was described in several studies (SESSO et al., 1990; STEENLAND et al., 1990; YAQOOB et al., 1992; NUYTS et al., 1995). However, these groups are rather broad, and no individual solvents or hydrocarbons could be identified as risk factors.

Furthermore, it must be kept in mind that solvents are used in combination with a wide category of other chemicals that are very difficult or virtually impossible to cover in an exposure assessment. This means that the term "solvents" or "hydrocarbons" would sometimes rather be an "indicator" for mixtures of substances occurring at a workplace, and, although cases had been exposed to solvents in their occupations, other chemicals might be responsible or contribute to the course of glomerulonephritis. This may be illustrated by a case report (BERNIS et al., 1985): In a patient suffering from Goodpasture's syndrome who was exposed to solvents as apprentice in a hairdressing salon, clinical remission was not observed after avoidance of solvents (hairsprays and paint solvents), but only after discontinuing (home) use of wavings containing thioglycolic acid. This patient would certainly have been classified as solvent-exposed in the case-control studies.

**Tab. 6.1** Exposure scoring system for estimation of occupational and non-occupational solvent and hydrocarbon exposure according to RAVNSKOV et al. (1979) and BELL (1985)\*.

| Exposure<br>(IF: intensity factor) | Activity with solvent or hydrocarbon fuel exposure   |
|------------------------------------|--|
| <b>Heavy</b><br>(IF 2)             | Occupational house painting indoors;<br>Industrial spray painting without protection devices;<br>Carpet cleaning and floor-covering cleaning agents;<br>Production of paint and glue;<br>Polystyrene plastic application;<br>Glue sniffing                                     |
| <b>Moderate</b><br>(IF 1)          | Non-occupational house painting indoors<br>Spray painting with protection devices<br>Industrial degreasing of metals<br>Printing work<br>Occupational glueing<br>Anaesthetic work<br>Dry cleaning<br>Varnishing<br>Fibre glass application<br>Hair sprays<br>Use of pesticides |
| <b>Slight</b><br>(IF 0.5)          | Outdoor painting<br>Motor repairing<br>Handling of petrol fuels<br>Hobby gluing<br>Drawing with felt-tipped pens<br>Exhaust fumes outdoors   |

\*: This system or slight modifications (as inclusion of additional activities) were used by RAVNSKOV et al. (1979); VAN DER LAAN (1980); BELL et al. (1985); PORRO et al. (1992); YAQOOB et al., (1992; 1993; 1994a,b); PAI et al. (1997, 1998); WAKAI et al. (1999).

### 6.2.2.3 Selection of control groups and recall bias

The selection of inappropriate control groups may introduce a bias. In this context, the use of hospital control groups (e.g. ZIMMERMAN et al., 1975; LAGRUE et al., 1977; FINN et al., 1980) has been criticized (PHILLIPS et al., 1998) because in such groups the employability in general (and therefore also at solvent-exposed workplaces) could be lower. This would introduce a bias that erroneously increases the association between hydrocarbon exposure and renal disease in the case group. However, in a number of studies (BELL et al., 1985; SESSO et al., 1990; PORRO et al., 1992; YAQOOB et al., 1992), hospital patient control groups suffered from minor and rather acute than chronic illnesses which are unlikely to have lowered their long-term employability. In other studies, in addition to hospital control groups, or exclusively, population-based control groups were used (STEENLAND et al., 1990; NUYTS et al., 1995; ASAL et al., 1996; WAKAI et al., 1999).

"Recall bias", i.e., the different accuracy of cases and controls to remember previous exposures, is a potential source of error in case-control studies which will lead to an inflation of the odds ratio (RAPHAEL, 1987).

The use of hospital or non-hospital patients suffering from chronic (renal or non-renal) disease other than GN may reduce this bias since it can be expected that these patients are likely to be just as eager to recall their exposure as the cases. However, as noted above, comparison with hospital patient control groups could introduce other bias.

A recall bias seems less likely when exposure is assessed by experts on the basis of the occupation reported by cases and controls. In such studies, it is reasonable to expect that the occupation will similarly be remembered. In several studies, an increased odds ratio was observed in groups of patients with occupational exposure, whereas no increase was found in non-occupationally (and less) exposed groups (see Tab. 6.2). This results suggest that a recall bias should not have been a major source of error.

Another way to check for possible recall bias is to ask for exposure to a "fake risk factor" which is not relevant with respect to the risk under study but for which exposure is of approximately equal plausibility (RAPHAEL, 1987). In this way, NUYTS et al. (1995) included exposure to asbestos (as a pollutant well-known in the population) and to aluminum (because of its relevance in treatment of patients with chronic renal failure). Similarly, STEENLAND et al. (1990) included exposure to ammonia as a check which was not thought to be related to kidney disease but may be well remembered due to its typical pungent odor. In both studies, odds ratios were not significant for these factors, suggesting that marked overreporting of exposure among cases may be unlikely.

To circumvent possible problems with "recall bias" and bias due to use of hospital patients, in two studies exposure was assessed from occupation by means of a public census day (RAVNSKOV et al., 1983; HARRISON et al., 1986). Since patients did not know about the suspected relation between hydrocarbon exposure and GN at the time of the census day, a recall bias probably can be excluded. The results of the study by RAVNSKOV et al. (1983) showed that the ratio of subjects with heavy hydrocarbon exposure was higher in the group of patients than in the control population, and there was a statistically significant dose-response relationship when the observed and expected ratios of patients were compared in each exposure category. HARRISON et al. (1986) estimated an "incidence" (cases per 100 000 per 20 years) retrospectively over the 20-year period during which the patients were recorded, and this "incidence" of GN was significantly greater for men employed in occupations with high exposure to solvents and heavy metals than for all other subgroups. However, analysis was not separately performed for hydrocarbon and heavy metal exposure in this study.

As occupation stated at the census day is only a rough estimate of exposure, an exposure misclassification cannot be ruled out. Indeed, RAVNSKOV et al. (1983) reported that information obtained later on showed 15 of 49 patients categorized in the lowest exposure group had previously been higher exposed. Such misclassifi-

cation might lead to an underestimation of risk because patients would erroneously be considered low or non-exposed.

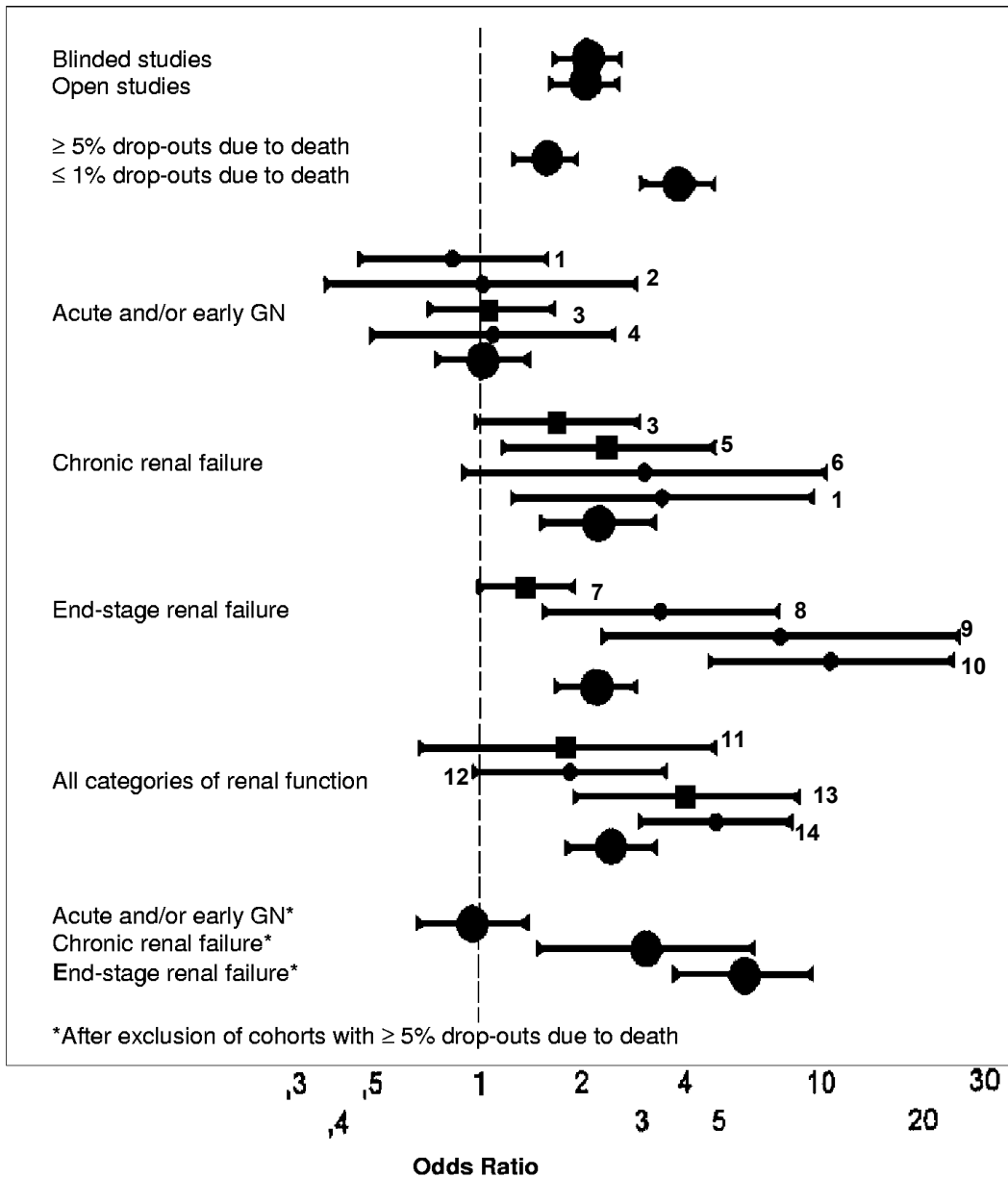
Altogether, although a recall bias cannot be excluded, it seems very unlikely that the observed associations between exposure and disease can be explained by the different designs of the studies.

#### 6.2.2.4 Interviewer bias (exposure suspicion bias)

A potential source of error could be an "interviewer bias" or "exposure suspicion bias" in studies in which the interviewer was not blinded to the status of the interviewed person. In this case, persons belonging to the case group might be asked more intensely about their exposure than those of the control group. In this way, exposure suspicion bias would lead to an overestimation of the odds ratio. On the other hand, it cannot be excluded that the effects may be underestimated if non-blinded interviewers doubt the underlying hypothesis.

An "exposure suspicion bias" cannot be ruled out in a number of studies in which at least the initial phase of the interview or exposure assessment was not "non-blinded". This group includes studies with positive (ZIMMERMAN et al., 1975; LAGRUE et al., 1977; RAVNSKOV, 1978; PORRO et al., 1992) as well as negative outcome (VAN DER LAAN, 1980; HARRINGTON, 1989; and likely also in the poorly described study of FRANCHINI et al., 1982). PORRO et al. (1992) state that though it was impossible to blind the interviewer to the disease status, this seems unlikely to have introduced a bias since the interviewer was unaware of the aims and design of the study. It is not clear if the complete questionnaire procedure was blinded in the (positive) study of SESSO et al. (1990), but the authors used a standardized, validated NIOSH questionnaire.

If only studies with "blinded" interviews are taken into account, the majority of them does show an increased odds ratio for solvent exposure. Moreover, the recently published meta-analysis of RAVNSKOV (2000a) has shown that the weighted mean odds ratios for studies with "blinded" and those with "non-blinded" interviews were identical (Fig. 6.1). Taken together, it seems unlikely that the reported associations can be explained by an "interviewer" or "exposure suspicion bias".



**Fig. 6.1** Graphical presentation of results from meta-analysis of case-control studies (graphic modified from RAVNSKOV, 2000a). Odds ratio (OR) for exposure in individual studies: small ●: OR for studies with < 1 % drop-outs; squares ■: OR for studies with ≥ 5 % dropouts due to death before questioning; large ●: mean weighted OR for various groupings of studies. Bars indicate 95 % confidence intervals.

1: STENGEL et al. (1995); 2: HARRINGTON et al. (1989); 3: ASAL et al. (1995); 4: VAN DER LAAN (1980); 5: NUYTS et al. (1995); 6: SESSO et al. (1990); 7: STEENLAND et al. (1990); 8: FINN et al. (1990); 9: ZIMMERMAN et al. (1975); 10: YAQOOB et al. (1992); 11: FRANCHINI et al. (1982); 12: PORRO et al. (1992); 13: RAVNSKOV et al. (1979); 14: LAGRUE et al. (1977).

### 6.2.3 Conclusions

Overall, taking into consideration the strengths and weaknesses of the different studies,

- the case-control studies show an association of chronic solvent exposure with glomerulonephritides;
- recall and interviewer bias are unlikely to explain the observed associations;
- no specific type of glomerulonephritis could be identified to be associated with solvent exposure;
- exposure to solvents may aggravate already existing (primary or systemic) glomerulonephritic disease;
- the observed odds ratio were higher
  - the more advanced the disease of the cases included in the study was (Fig. 6.1),
  - the higher intensity, frequency and duration of exposure (assessed by scores) were; and
  - when the rate of drop-out due to death was low (Fig. 6.1);
- no individual solvents could be identified as risk factors.

**Tab. 6.1** Diagnostic classification of glomerulonephritis in case groups of case-control studies\*.

| No. of biopsy-proven cases with diagnostic classification |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           | Reference |                          |                |                     |           |                         |                 |            |                |                        |                           |                       |                            |                    |                          |                         |
|---|---------------------------|-----------------------|------------------|-------------|--------------------------|-------------------------------------|----------------------|--------------------|-----------------------------|-----------------------------|------------------------|---------------------------|-----------|--------------------------|----------------|---------------------|-----------|-------------------------|-----------------|------------|----------------|------------------------|---------------------------|-----------------------|----------------------------|--------------------|--------------------------|-------------------------|
| Focal segmental   | Fibrillary glomerulopathy | Diffuse proliferative | Not classifiable | Other types | Normal or minimal lesion | Minimal change and FSH <sup>a</sup> | Chronic non-specific | Mesangio-capillary | Endocapillary proliferative | Focal ischemia or sclerosis | Mesangio-proliferative | Global glomerulosclerosis |           | Focal glomerulosclerosis | Extracapillary | Focal proliferative | Exudative | Acute poststreptococcal | IgA-nephropathy | Membranous | Minimal lesion | Membrano-proliferative | Extracapillary crescentic | Prolif. (not further) | No. of biopsy-proven cases | Total no. of cases |                          |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         |                 |            |                |                        |                           |                       | 12                         | 28                 | ZIMMERMAN et al. (1975)  |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         | 48              | 35         | 65             | 39                     |                           |                       |                            | 187                | 247                      | LAGRUE et al. (1977)    |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     | 9         |                         |                 |            |                |                        |                           |                       | 9                          | 15                 | RAVNSKOV et al. (1978)   |                         |
|   |                           |                       | 4                |             |                          |                                     |                      |                    |                             |                             |                        |                           | 2         | 2                        | 19             | 1                   |           |                         | 1               | 6          | 4              |                        |                           |                       | 50                         | 50                 | RAVNSKOV et al. (1979)   |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        | 1                         | 7         |                          |                |                     |           |                         | 9               | 6          | 8              |                        |                           |                       | 50                         | 50                 | VAN DER LAAN (1980)      |                         |
|   |                           |                       | 2                |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         | 4               |            |                |                        | 2                         |                       | 14                         | 37                 | FINN et al. (1980)       |                         |
|   |                           |                       |                  | 8           |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         | 28              | 9          | 24             |                        |                           |                       | 116                        | 116                | FRANCHINI et al. (1982)  |                         |
|   |                           |                       | 17               |             |                          |                                     |                      |                    |                             | 9                           |                        |                           |           |                          | 7              | 2                   |           |                         | 9               |            | 12             |                        |                           |                       | 124                        | 124                | RAVNSKOV et al. (1983)   |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         |                 |            |                |                        |                           |                       | 50                         | 50                 | BELL et al. (1985)       |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         | 73              |            |                |                        |                           |                       | 73                         | 73                 | HARRISON et al. (1986)   |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         | d               | 8          | d              |                        |                           |                       | 50                         | 50                 | HARRINGTON et al. (1989) |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         |                 |            |                |                        | 17                        |                       | 17                         | 17                 | SESSO et al. (1990)      |                         |
|   |                           |                       |                  |             |                          |                                     |                      |                    |                             |                             |                        |                           |           |                          |                |                     |           |                         |                 |            |                |                        |                           |                       |                            | 325 <sup>c</sup>   |                          | STEENLAND et al. (1990) |



| No. of biopsy-proven cases with diagnostic classification |                            |                       |                           |                        |                |            |                 |                         |           |                     |                |                          |                           |                        |                             |                             |                    |                      | Reference |                                     |                          |             |                  |                       |                           |                 |                       |
|---|----------------------------|-----------------------|---------------------------|------------------------|----------------|------------|-----------------|-------------------------|-----------|---------------------|----------------|--------------------------|---------------------------|------------------------|-----------------------------|-----------------------------|--------------------|----------------------|-----------|-------------------------------------|--------------------------|-------------|------------------|-----------------------|---------------------------|-----------------|-----------------------|
| Total no. of cases  | No. of biopsy-proven cases | Prolif. (not further) | Extracapillary crescentic | Membrano-proliferative | Minimal lesion | Membranous | IgA-nephropathy | Acute poststreptococcal | Exudative | Focal proliferative | Extracapillary | Focal glomerulosclerosis | Global glomerulosclerosis | Mesangio-proliferative | Focal ischemia or sclerosis | Endocapillary proliferative | Mesangio-capillary | Chronic non-specific |           | Minimal change and FSH <sup>a</sup> | Normal or minimal lesion | Other types | Not classifiable | Diffuse proliferative | Fibrillary glomerulopathy | Focal segmental |                       |
| 60  | 60                         |                       | 1                         | 4                      | 4              | 6          | 27              |                         |           |                     |                | 7                        |                           | 5                      |                             | 6                           |                    |                      |           |                                     |                          |             |                  |                       |                           |                 | PORRO et al. (1992)   |
| 55  | 55                         | 40                    |                           |                        |                | 3          |                 |                         |           |                     |                |                          |                           |                        |                             |                             | 5                  | 7                    |           |                                     |                          |             |                  |                       |                           |                 | YAQOOB et al. (1992)  |
| 29  | 29                         | 60                    |                           |                        |                | 8          |                 |                         |           |                     |                |                          |                           |                        |                             |                             |                    |                      |           |                                     |                          |             |                  |                       |                           |                 | YAQOOB et al. (1993)  |
| 59  | 59                         |                       |                           |                        |                | 7          |                 |                         |           | 16                  |                |                          |                           | 36                     |                             |                             |                    |                      |           |                                     |                          |             |                  |                       |                           |                 | YAQOOB et al. (1994a) |
| 298   | 298                        |                       |                           |                        |                | 82         | 116             |                         |           |                     |                |                          |                           |                        |                             |                             |                    |                      | 100       |                                     |                          |             |                  |                       |                           |                 | STENGEL et al. (1995) |
| 321   | 249                        |                       | 9                         | 4                      | 19             | 57         | 38              |                         |           | 6                   |                | 76                       |                           | 14                     |                             |                             |                    |                      |           |                                     |                          | 4           | 22               | 3                     | 1                         |                 | ASAL et al. (1996)    |
| 41  | 41                         |                       |                           | 1                      |                | 11         |                 |                         |           |                     |                |                          |                           | 17                     |                             |                             |                    |                      |           |                                     |                          |             |                  |                       | 12                        |                 | PAI et al. (1997)     |
| 28  | 28 <sup>b</sup>            |                       |                           |                        |                |            |                 |                         |           |                     |                |                          |                           |                        |                             |                             |                    |                      |           |                                     |                          |             |                  |                       |                           |                 | PAI et al. (1998)     |
| 94  | 94                         |                       |                           |                        |                |            | 94              |                         |           |                     |                |                          |                           |                        |                             |                             |                    |                      |           |                                     |                          |             |                  |                       |                           |                 | WAKAI et al. (1999)   |

\*: as given in the corresponding original reference. Only studies in which GN was investigated are included.

#: including cases with Goodpasture's syndrome;

a: FSH: focal glomerulosclerosis and hyalinosis

b: patients were diagnosed with GN due to systemic vasculitis (Wegener's granulomatosis or microscopic polyangiitis).

c: cases were taken from kidney disease registry, suffering from ESRD due to GN, nephrosclerosis or interstitial kidney disease, only about 5 % biopsied.

d: various types of acute GN diagnosed (40 % had proliferative GN) but exact number cannot be derived from reported data.

**Tab. 6.2** Nephrotoxicity of hydrocarbon solvents – case-control studies

| Cases   | Controls   | Exposure   |                                      | Odds ratio<br>(95 % confidence interval) | Remarks   | Reference                                    |
|---|--|--|--------------------------------------|--|---|--|
|   |  | Measure <sup>#</sup>   | Kind                                 |  |   |  |
| 28 (24, 4)<br>31 – 68 a<br>GN, non-systemic, proliferative,<br>biopsy-proven (n=12) or suspected (n=16)<br>Advanced renal failure,<br>creatinine clearance<br>< 15 ml/min | I: 35 (21,11)<br>(no data)<br>patients with other renal diseases   | Interview,<br>non-blinded;<br>11-point scale (0 – 10) (d, f) | Any to solvents,<br>other chemicals? | <b>7.5<sup>b</sup></b><br>(2.2 – 24.5)   | Exposure measure:<br>including other<br>chemicals (e.g.<br>metals)<br>score for cases ↑<br>than in both control<br>groups                 | ZIMMER-<br>MAN et al.<br>(1975)              |
|   | II: no data<br>no data<br>hospital patients without renal<br>diseases; matched by age, sex                           |  |                                      |  |   |  |
| 247 (189, 58)<br>< 20 – > 60 a (50 % 20 – 40 a)<br>GN, primary, 76 % biopsy-<br>proven, various<br>No data on renal function  | I: 124 (94, 30)<br>(40 % 20 – 40 a)<br>hospital patients (hypertension,<br>urinary infection, kidney stones)         | Interview,<br>non-blinded;<br>11-point scale (0 – 10) (d, f) | Any to solvents,<br>other chemicals  | <b>4.9<sup>b</sup></b><br>(2.9 – 8.0)    | Exposure measure:<br>including other<br>chemicals (esp.<br>metals)<br>score for cases ↑<br>than for controls<br>(only subgroup<br>tested) | LAGRUE<br>(1976);<br>LAGRUE et<br>al. (1977) |
|   | II: 29 (no data)<br>(no data)<br>patients with secondary<br>glomerular<br>damage;<br>"matched" (no details reported) |  |                                      |  |   |  |

| Cases   | Controls  | Exposure   |  | Odds ratio<br>(95 % confidence interval) | Remarks  | Reference   |
|---|---|--|--|--|--|---|
|   |   | Measure <sup>#</sup>   | Kind   |  |  |   |
| <p>No. (m, f)<br/>Age<br/>Diagnosis<br/>Renal function</p>  | <p>No. (m, f)<br/>Age<br/>Population<br/>Matching criteria</p>  |  |  |  |  |   |
| <p>15 (13, 2)<br/>4 – 61 a (n=9 under 16 a)<br/>GN, acute poststreptococcal<br/>serum creatinine 50 – 1250 µM<br/>(5.6 – 141 mg/l) at onset of<br/>disease</p>                                  | <p>15 (13, 2)<br/>(no data)<br/>patients infected with group A β-<br/>hemolytic streptococci;<br/>matched by age, sex</p>   | <p>Interview,<br/>non-blinded;<br/>subjective, poorly<br/>defined cate-<br/>gories</p>       | <p>Organic solvents<br/>(paints, but no<br/>details reported)</p>  | <p>Not reported</p>                      | <p>Exposure measure:<br/>no details reported,<br/>10 cases, but no<br/>controls "signifi-<br/>cantly" exposed</p>  | <p>RAVN-<br/>SKOV<br/>(1977);<br/>RAVN-<br/>SKOV<br/>(1978)</p> |
| <p>50 (34, 16)<br/>32 (17 – 65) a<br/>GN, biopsy-proven, mostly (96<br/>%) primary<br/>no hemodialysis patients,<br/>median serum creatinine 100<br/>µM (11.3 mg/l),<br/>GFR &gt; 30 ml/min</p> | <p>I: 50 (34, 16)<br/>31 (16 – 66) a<br/>hospital patients with non-<br/>glomerular renal disease (median<br/>serum creatinine 90 µM)<br/>II: 50 (34, 16)<br/>31 (16 – 66) a<br/>hospital patients with appendicitis;<br/>matched by age (± 5 a), sex</p> | <p>Questionnaire +<br/>interview,<br/>non-blinded;<br/>exposure score<br/>(d, f, i)</p>      | <p>Occupational and<br/>non-occupa-<br/>tional, various<br/>activities (esp.<br/>painting, degrea-<br/>sing, gluing),<br/>exposure score<br/>&gt; 10</p> | <p><b>3.9</b><br/>(1.9 - 8.1)</p>        | <p>Score for cases ↑<br/>than for both control<br/>groups;<br/>OR estimated for<br/>matched triplets (1<br/>case, 2 controls);<br/>some indication of<br/>dose-response<br/>relationship</p> | <p>RAVN-<br/>SKOV et al.<br/>(1979)</p>                         |
| <p>50 (34, 16)<br/>42 (15 – 70) a<br/>GN, various types, biopsy-<br/>proven;<br/>early stage of chronic renal<br/>disease, no ESRD</p>  | <p>50 (no data)<br/>(no data)<br/>outpatients (various internal<br/>diseases) from same hospitals<br/>matched by age, sex, hospital</p>   | <p>Questionnaire +<br/>interview,<br/>blinded;<br/>11-point scale<br/>(0 – 10) (d, f, i)</p> | <p>Organic solvents,<br/>higher exposure</p>   | <p>1.1<br/>(0.4 – 2.4)<sup>b</sup></p>   | <p>Score for cases and<br/>controls similar for<br/>both control groups</p>  | <p>VAN DER<br/>LAAN<br/>(1980)</p>                              |

| Cases  | Controls  | Exposure   |  | Odds ratio<br>(95 % confidence interval)      | Remarks  | Reference                          |
|--|---|--|--|---|--|------------------------------------|
|  |   | Measure <sup>#</sup>   | Kind                                   |   |  |                                    |
| <p>No. (m, f)<br/>Age<br/>Diagnosis<br/>Renal function</p>   | <p>No. (m, f)<br/>Age<br/>Population<br/>Matching criteria</p>  |  |  |   |  |                                    |
| <p>37 (30, 7)<br/>no data<br/>GN, 38 % biopsy-proven, non-systemic<br/>ESRD, hemodialysis</p>                    | <p>I: 52 (29, 23)<br/>no data<br/>hemodialysis patients due to non-GN renal diseases<br/>II: 53 (53, -)<br/>20 – 65 a<br/>hospital inpatients, no renal disease<br/>"to match the hemodialysis patients"<br/>(no further data reported)</p> | <p>Questionnaire,<br/>blinded?;<br/>dichotomous<br/>scale (exposure<br/>defined as<br/>≥ 2 h/d, 5 d/w,<br/>2 a) (d, f)</p> | <p>Hydrocarbon-based<br/>compounds</p> | <p><b>3.4<sup>b</sup></b><br/>(1.5 – 7.3)</p> | <p>OR relative to<br/>combined controls;<br/>exposure prevalence<br/>↑ for cases than for<br/>control I and (male<br/>only) control II</p>   | <p>FINN et al.<br/>(1980)</p>      |
| <p>116 (no data)<br/>41.0 ± 14.8 a (&gt; 16 a)<br/>GN, biopsy-proven, chronic;<br/>no data on renal function</p> | <p>no data<br/>no data<br/>hospital patients with a broad range<br/>of injuries and diseases<br/>matched by age, sex</p>  | <p>Not strictly standardized: questionnaire or interview;<br/>blinded?<br/>11-point scale (d, f, i)</p>                    | <p>Organic solvents</p>                | <p>1.5<br/>(0.5 – 4.2)</p>                    | <p>Information in 7 % of<br/>cases collected from<br/>relatives of deceased<br/>patient<br/>higher exposure<br/>score in subgroup<br/>with membranous<br/>GN (no details<br/>reported)</p> | <p>FRANCHINI<br/>et al. (1982)</p> |

| Cases   | Controls  | Exposure   |   | Odds ratio<br>(95 % confidence interval) | Remarks   | Reference                      |
|---|---|--|---|--|---|--------------------------------|
|   |   | Measure <sup>#</sup>   | Kind  |  |   |                                |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>  | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |  |   |  |   |                                |
| 124 (88, 36)<br>16 – 74 a<br>GN, acute or chronic, primary,<br>biopsy-proven, non-systemic;<br>no data on renal function  | no data<br>no data<br>economically active persons within<br>general population from same area   | Occupation at<br>public census in<br>1975;<br>4-point scale (i)          | Occupational,<br>organic solvents<br>or fuels | Not reported                             | "Most patients with<br>ESRD excluded";<br>no. of exposed sub-<br>jects ↑ in patient<br>group, dose re-<br>sponse relationship | RAVN-<br>SKOV et al.<br>(1983) |
| 50 (40, 10)<br>31 ± 2 a<br>GN, biopsy-proven, non-<br>systemic, proliferative<br>no data on renal function  | 100 (80, 20)<br>(no data)<br>acute hospital admissions (various<br>diagnoses, no renal disease) from<br>same region<br>matched by age (± 3 a), sex, social<br>class | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, f, i) | Occupational,<br>solvents                     | Not reported                             | Exposure measure:<br>ordinal scale,<br>score for case ↑ than<br>for control group   | BELL et al.<br>(1985)          |
|   |   |  | Non-<br>occupational,<br>solvents             | Not reported                             | Exposure score simi-<br>lar for case and<br>control group   |                                |
| all: 73 (53, 20)<br>45 (9 – 75) a<br>"high exposure": 27 (26, 1)<br>"low exposure": 37 (23, 14)<br>GN, biopsy-proven, idiopathic<br>membranous;<br>nephrotic syndrome | no control group  | Occupation at<br>public census in<br>1971;<br>high/low<br>exposure       | Organic solvents,<br>heavy metals             | (Inapplicable)                           | Estimated incidence<br>of GN ↑ in "high<br>exposure" than in<br>"low exposure<br>group"; exposure not<br>solvent-specific     | HARRISON<br>et al. (1986)      |

| Cases  | Controls  | Exposure   |   | Odds ratio<br>(95 % confidence interval)   | Remarks  | Reference                        |
|--|---|--|---|--|--|----------------------------------|
|  |   | Measure <sup>#</sup>   | Kind  |  |  |                                  |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>   | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |  |   |  |  |                                  |
| 50 (37, 13)<br>47.5 ± 14.8 (20 – 79) a<br>GN, biopsy-proven acute  | 50 (37, 13)<br>47.8 ± 14.8 a (22 – 79 a)<br>general population, same community<br>matched by age (± 5 a), sex,<br>ethnicity, socioeconomic group,<br>residential area | Questionnaire +<br>interview,<br>non-blinded;<br>exposure score<br>(d, i)              | any solvent expo-<br>sure (mostly fuels<br>and oils, degrea-<br>sing agents,<br>paint, varnishes,<br>glues)                                 | 1.0<br>(0.16 – 6.3)  | Only 9 cases<br>classified "exposed"<br>(score ≥ 100)  | HARRING-<br>TON et al.<br>(1989) |
| 325 (325, –)<br>30 – 69 a<br>GN, nephrosclerosis, interstitial<br>kidney disease, < 5 % of cases<br>biopsied<br>ESRD | 325 (325, –)<br>(no data)<br>general population<br>matched by age (± 5 a), race, sex,<br>residential area   | Interview;<br>exposure from<br>occupation<br>according to US<br>census code, (d,<br>f) | Occupational,<br>All solvents<br><hr/> Paints and<br>glues<br><hr/> Cleaning/<br>degreasing<br><hr/> Solvents<br>used in other<br>processes | <b>1.51</b><br>(1.03 – 2.22)<br><br>1.01<br>(0.58 – 1.74)<br><br><b>2.50</b><br>(1.56 – 3.95)<br><br>1.05<br>(0.44 – 2.48) | Evaluation of Kidney<br>Disease Registry for<br>cases with ESRD,<br><br>High drop-out rate<br>because of death<br>prior to study inter-<br>view and because of<br>non-responding | STEEN-<br>LAND et al.<br>(1990)  |

| Cases   | Controls  | Exposure  |                              | Odds ratio<br>(95 % confidence interval) | Remarks                                   | Reference                       |
|---|---|---|------------------------------|--|---|---------------------------------|
|   |   | Measure <sup>#</sup>  | Kind                         |  |   |                                 |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>  | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |   | Occupational,<br>oil and gas | 0.74<br>(0.64 – 1.51)                    |   | STEEN-<br>LAND et al.<br>(1990) |
| 17 (13, 4)<br>41.0 ± 17.1 (15 – 69) a<br>GN, biopsy-proven non-systemic crescentic rapidly progressive RF, creatinine clearance < 25 ml/min 2 weeks after onset of symptoms | 34<br>(no data)<br>patients at surgical wards (acute illness or minor surgery, normal renal function)<br>matched by age (± 5 a), sex<br>(2 controls/case)   | Questionnaire, blinded ?;<br>exposure defined as ≥ 1 h/w for 3 consecutive months | Overall hydrocarbons         | 2.8<br>(0.71 – 11.07)                    |   | SESSO et al. (1990)             |
|   |   |   | Organic solvents             | <b>5.0</b><br>(1.14 – 22.0)              |   |                                 |
|   |   |   | Fuels                        | 3.3<br>(0.76 – 13.89)                    |   |                                 |
| 60 (44, 16)<br>27.5 ± 11.7 (≥ 14) a<br>GN, biopsy-proven non-systemic, chronic<br>no data on renal function reported  | 120 (2 groups)<br>28.0 ± 11.9 (≥ 14) a<br>I: 60 outpatients with traumatic fractures, no signs of nephropathy<br>II: 60 outpatients with nephrolithiasis from same province, matched by age (± 5 a), sex (1 patient from each control group/case) | Questionnaire + interview, blinded <sup>+</sup> ;<br>exposure score (d, f, i)     | Any solvent exposure         | 1.86<br>(0.96 – 3.54)                    | Exposure score ↑<br>than in both controls | PORRO et al. (1992)             |

| Cases  | Controls   | Exposure             |                                   | Odds ratio<br>(95 % confidence interval) | Remarks                                      | Reference           |
|--|--|----------------------|-----------------------------------|--|--|---------------------|
|  |  | Measure <sup>#</sup> | Kind                              |  |  |                     |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>   | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b> |                      |                                   |  |  |                     |
|  |  |                      | Occupational solvent exposure     | <b>3.9</b><br>(1.64 – 8.33)              | Exposure score ↑ than in both controls;      | PORRO et al. (1992) |
|  |  |                      | Lower exposure                    | 2.12<br>(0.81 – 5.57)                    | OR calculated relative to non-exposed;       |                     |
|  |  |                      | Higher exposure                   | <b>5.42</b><br>(2.01 – 14.59)            | OR showed significant exposure-related trend |                     |
|  |  |                      | Non-occupational, high exposure   | 0.78<br>(0.29 – 2.11)                    | Exposure score not different from controls   |                     |
| 27 (21, 6)   | 54 (see above)   |                      | Any solvent exposure              | <b>3.50</b><br>(1.18 – 12.18)            | Exposure score ↑ than in both controls       |                     |
| not reported subgroup with IgA-nephropathy; no data on renal function reported |  |                      | Occupational solvent exposure     | <b>4.25</b><br>(1.18 – 16.36)            | Exposure score ↑ than for control I          |                     |
|  |  |                      | Non-occupational solvent exposure | 1.71<br>(0.57 – 4.94)                    | Exposure score not different from controls   |                     |



| Cases   | Controls  | Exposure   |  | Odds ratio<br>(95 % confidence interval)   | Remarks  | Reference                |
|---|---|--|--|--|--|--------------------------|
|   |   | Measure <sup>#</sup>   | Kind   |  |  |                          |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>  | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |  |  |  |  |                          |
| 55 (41, 14)<br>46.4 ± 12.3 (20 – 70) a<br>GN, biopsy-proven, primary;<br>ESRD   | I: 45 (24, 21)<br>43 ± 12 (20 – 69) a<br>patients with ESRD of various<br>other etiology<br>II: 55 surgical day unit patients<br>(minor complaints, no renal disease)<br>matched by age (± 2 a), sex, social<br>class, residential area | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, f, i) | Petroleum<br>products<br><br>Greasing/degreas-<br>ing agents<br><br>Paints and glues<br><br>Combined | <b>15.5</b><br>(not reported)<br><br><b>5.3</b><br>(not reported)<br><br><b>2.0</b><br>(not reported)<br><br><b>10.5<sup>b</sup></b><br>(4.6 – 23.5) | Total hydrocarbon-<br>score ↑ than for<br>controls I and II;<br><br>No differences in<br>smoking and drinking<br>habits  | YAQOOB et<br>al. (1992)  |
| 29 (24, 5)<br>47 ± 2.2 a<br>GN, biopsy-proven, primary;<br>PRF, persistent rise of serum<br>creatinine > 50 μM (≥ 5.6 mg/l)<br>above baseline | 39 (32, 7)<br>42 ± 5.5 a<br>patients with GN similar to cases, but<br>with non-PRF  | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, f, i) | Overall<br>hydrocarbon<br>exposure   | Not reported   | Total hydrocarbon-<br>score ↑ for case<br>group after "follow-<br>up" period (mean:<br>5 a) course of<br>disease much less<br>favorable in group<br>with initial PRF | YAQOOB et<br>al. (1993a) |

| Cases   | Controls  | Exposure   |  | Odds ratio<br>(95 % confidence interval) | Remarks   | Reference                |
|---|---|--|--|--|---|--------------------------|
|   |   | Measure <sup>#</sup>   | Kind                                     |  |   |                          |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>  | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |  |  |  |   |                          |
| 24 (21, 3)<br>46 ± 2.4 a<br>GN, biopsy-proven, primary;<br>PRF: serum creatinine<br>> 100 µM (11.3 mg/l) above<br>baseline levels | 35 (29, 6)<br>43 ± 2.7 a<br>age-, sex-matched patients with GN<br>similar to cases, but with non-PRF  | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, f, i) | Overall<br>hydrocarbon<br>exposure       | <b>12.8</b><br>(3.0 – 52.6)              | Total hydrocarbon-<br>score ↑ for case<br>group with PRF  | YAQOOB et<br>al. (1994a) |
| 37 (20, 17)<br>48.3 ± 2.2 a<br>type I diabetes,<br>incipient diabetic nephropathy   | 45 (22, 23)<br>44.2 ± 2.1 a<br>type I diabetics without nephropathy;<br>matched by age, sex, duration of<br>diabetes, recent glycaemic control,<br>social class, residential area | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, f, i) | Overall<br>hydrocarbon,<br>high exposure | <b>3.7<sup>a</sup></b><br>(1.3 – 10.1)   | Total hydrocarbon-<br>score ↑ for case<br>group<br>score ↑ for patients<br>with<br>microalbuminuria | YAQOOB et<br>al. (1994b) |
| 31 (16, 15)<br>45.1 ± 2.1 a<br>type I diabetes,<br>overt diabetic nephropathy   |   |  | Overall<br>hydrocarbon,<br>high exposure | <b>5.2<sup>a</sup></b><br>(1.8 – 14.9)   | Total hydrocarbon-<br>score ↑ for case<br>group   |                          |

| Cases  | Controls  | Exposure   |   | Odds ratio<br>(95 % confidence interval)   | Remarks  | Reference                   |
|--|---|--|---|--|--|-----------------------------|
|  |   | Measure <sup>#</sup>   | Kind  |  |  |                             |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>   | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |  |   |  |  |                             |
| 272 (159, 113)<br>59.9 (20 – 88) a<br>CRF, different diagnostic classifications;<br>creatinine clearance < 3 <sup>rd</sup> percentile of normal distribution,<br>30 % dialysis patients (ESRD) | 272 (159, 113)<br>59.6 (23 – 86) a<br>general population;<br>matched by age, sex, region of residence                                 | Interview,<br>blinded;<br>occupational exposure score<br>(d, f, i)                 | Occupational,<br>hydrocarbons overall<br><br>oxygenated hydrocarbons<br><br>aromatic hydrocarbons<br><br>aliphatic hydrocarbons | ca. 1.4*<br>(ca. 0.9 – 2.2)<br><br><b>5.45</b><br>(1.84 – 16.2)<br><br>ca. 2.1*<br>(ca. 0.6 – 6.2)<br><br>ca. 5.8*<br>(ca. 0.6 – 48.6) | Exposure measure:<br>ordinal scale,<br>average frequency of solvent exposure ↑<br>within group of patients with GN | NUYTS et al. (1995)         |
| 298 (191, 107)<br>≥ 18 a<br>GN, different diagnostic classifications, primary, biopsy-proven;<br>no details on renal function noted  | 298 (191, 107)<br>hospital patients with various chronic and acute diseases;<br>matched by age (± 5 a), sex, origin, residential area | Questionnaire + interview,<br>blinded;<br>occupational exposure score<br>(d, f, i) | Any solvents,<br>low or < 2 h/week exposure<br><br>Any solvents,<br>high or > 2 h/week exposure                                 | 1.0<br>(0.6 – 1.6)<br><br>1.2<br>(0.7 – 2.1)   | OR refer to men (OR for women not shown in study because of small number of exposed women)                         | STENGEL et al. (1995, 1996) |

| Cases  | Controls   | Exposure   |  | Odds ratio<br>(95 % confidence interval) | Remarks   | Reference                         |
|--|--|--|--|--|---|-----------------------------------|
|  |  | Measure <sup>#</sup>   | Kind   |  |   |                                   |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>   | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b> |  |  |  |   |                                   |
| 17 (17, -)<br>not reported<br>minimal change nephropathy or<br>focal/segmental hyalinosis;<br>CRF, serum creatinine > 150<br>$\mu\text{M}$ ( $\geq 17$ mg/l) | 57 (m)<br>not reported<br>see above  | Questionnaire +<br>interview,<br>blinded;<br>occupational<br>exposure score<br>(d, f, i) | Any solvents,<br>low or < 2 h/week<br>exposure   | 0.9<br>(0.2 – 10.1)                      | Subgroup of<br>patients;<br>OR also increases<br>with duration of<br>exposure | STENGEL<br>et al. (1995,<br>1996) |
|  |  |  | Any solvents,<br>high or > 2 h/<br>week exposure | 7.7<br>(1.4 – 41.6)                      |   |                                   |
| 36 (36, -)<br>not reported<br>IgA-nephropathy;<br>CRF, serum creatinine<br>> 150 $\mu\text{M}$ ( $\geq 17$ mg/l)   | 57 (m)<br>not reported<br>see above  | Questionnaire +<br>interview,<br>blinded;<br>occupational<br>exposure score<br>(d, f, i) | Any solvents,<br>low or < 2 h/week<br>exposure   | 1.2<br>(0.4 – 3.4)                       | Subgroup of<br>patients;<br>OR also increases<br>with duration of<br>exposure |                                   |
|  |  |  | Any solvents,<br>high or > 2 h/<br>week exposure | 3.5<br>(1.0 – 11.8)                      |   |                                   |

| Cases   | Controls  | Exposure  |                                    | Odds ratio<br>(95 % confidence interval) | Remarks   | Reference                                   |
|---|---|---|------------------------------------|--|---|---|
|   |   | Measure <sup>#</sup>  | Kind                               |  |   |   |
| 321 (186, 135)<br>18 – 79 a<br>glomerulopathies, primary idiopathic chronic, various underlying diseases, 78 % biopsy-proven;<br>with or without ESRD, n=20 with proteinuria > 2 g/d, no detailed data<br>high drop-out (n=51 of initially n=496, i.e. 10 %) due to death (no details reported) | 321 (186, 135)<br>not reported<br>general population<br>age (± 5 a), sex, geographical area | Questionnaire + interview, blinded;<br>occupational lifetime exposure assessment;;<br>estimated hc-exposure (mean/median) ppm:<br>cases: 165/48<br>contr.: 162/43 | Occupational, hydrocarbons overall | 1.39<br>(0.94 – 2.04)                    | Exposure measure: hydrocarbon score as dichotomous variable, cut-off at 100 ppm                             | ASAL et al. (1996);<br>NELSON et al. (1995) |
|   |   |   | Occupational, hydrocarbons overall | not reported                             | Exposure measure: ordinal scale, score mean and frequency distribution not different for cases and controls |   |
| 111 (not reported)<br>not reported<br>various<br>serum creat. > 40 mg/l (354 µM)  | 111 (not reported)  |   | Occupational, hydrocarbons overall | <b>2.40</b><br>(1.18 – 4.90)             | Exposure measure: dichotomous scale; subgroup of patients   |   |

| Cases  | Controls  | Exposure   |   | Odds ratio<br>(95 % confidence interval) | Remarks  | Reference            |
|--|---|--|---|--|--|----------------------|
|  |   | Measure <sup>#</sup>   | Kind  |  |  |                      |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>   | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |  |   |  |  |                      |
| 41 (30, 11)<br>(not reported)<br>GN, biopsy-proven, primary,<br>non-IgA<br>no data on renal function   | 60 (46, 14)<br>(not reported)<br>blood donors (no evidence of renal<br>diseases)<br>matched by sex  | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, f, i) | Occupational and<br>non-<br>occupational, any<br>solvents | Not reported                             | Mean, median, and<br>range of solvent<br>exposure score ↑<br>within case group;<br>no overall differences<br>in genetic variants of<br>microsomal metabolism | PAI et al.<br>(1997) |
| 28 (19, 9)<br>20 – 73 a<br>GN, idiopathic crescentic<br>necrotizing, primary, MPA, WG<br>n=11: serum creat. 200 – 705<br>μM, n=12: hemodialysis, n=5:<br>no data | 28 (19, 9)<br>not reported<br>blood donors (n=15) or acute<br>medical patients (60 - 73 a) from<br>same area;<br>matched by age (± 3 a), sex, social<br>class | Questionnaire +<br>interview,<br>blinded;<br>exposure score<br>(d, i)    | Occupational and<br>non-<br>occupational, any<br>solvents | Not reported                             | Mean, median, and<br>range of solvent<br>exposure score ↑<br>within case group   | PAI et al.<br>(1998) |

| Cases  | Controls  | Exposure  |                                  | Odds ratio<br>(95 % confidence interval) | Remarks  | Reference              |
|--|---|---|----------------------------------|--|--|------------------------|
|  |   | Measure <sup>#</sup>  | Kind                             |  |  |                        |
| <b>No. (m, f)</b><br><b>Age</b><br><b>Diagnosis</b><br><b>Renal function</b>   | <b>No. (m, f)</b><br><b>Age</b><br><b>Population</b><br><b>Matching criteria</b>  |   |                                  |  |  |                        |
| 94 (48, 46)<br>20 – 69 a<br>m: 38.0 ± 12.4 a;<br>f: 39.6 ± 13.5 a<br>IgA-nephropathy, biopsy-proven, non-systemic<br>no data on renal function | 185 (93, 92)<br>m: 38.1 ± 12.1 a; f: 39.4 ± 13.3 a<br>general population<br>matched by age (± 2 a), sex,<br>residential area (2 controls/ case) | Questionnaire,<br>blinded;<br>occupational<br>exposure (no<br>details reported) | Work-related<br>solvent exposure | 0.55<br>(0.27 – 1.12)                    | Only few patients<br>(no. not given) with<br>advanced renal<br>failure | WAKAI et<br>al. (1999) |
| Subgroup (no. not reported)<br>serum creat. < 15 mg/l<br>(< 133 µM)  |   |   |                                  | 0.54<br>(0.23 – 1.26)                    |  |                        |
| Subgroup (no. not reported)<br>serum creat. > 15 mg/l<br>(> 133 µM)  |   |   |                                  | 0.35<br>(0.07 – 1.73)                    |  |                        |

**Bold symbols** indicate statistically significant difference compared to data for corresponding control group.

<sup>#</sup>: consideration of d: duration, f: frequency, and i: intensity of exposure in the corresponding study is indicated in brackets;

\*: values estimated from figure;

<sup>†</sup>: interviewer was unaware of study hypothesis and design, but not blind about patient status;

a: smoking-adjusted OR;

b: values not reported in the original reference, but calculated by RAVNSKOV (2000a) based on data given in the original study or from further information requested from the authors of the original study;

c: values not reported in the original reference, but calculated by DANIELL et al. (1988).

## 6.3 Cross-sectional studies

### 6.3.1 Description of studies

Reviews on cross-sectional studies are available from BERNARD and LAUWERYS (1989), HOTZ and BOILLAT (1989), HOTZ (1994), and MUTTI (1996).

#### Solvents and workplaces

Cross-sectional studies have been carried out in groups of workers exposed to

- mixed solvents (GRUENER et al., 1992; HOTZ et al., 1989, 1990, 1993, 1997; MEYER et al., 1984; NORMAND et al., 1989, 1990; PAI et al., 1996, 1998; STEVENSON et al., 1995; YAQOUB et al., 1993; ZSCHIESCHE and TRIEBIG, 1990);
- hydrocarbon mixtures such as white spirit and mineral oils (HASHIMOTO et al., 1991; KRUSELL et al., 1985; LAUWERYS et al., 1985; MUTTI et al., 1981; PAI et al., 1996, 1998; PRICE, 1994; ROCSKAY et al., 1991; STEVENSON et al., 1995; VIAU et al., 1987; VYSKOCIL et al., 1991; YAQOUB et al., 1983, 1993);
- toluene or toluene/xylene mixtures (ASKERGREN et al., 1981a,b,c,d; FRANCHINI et al., 1983; LAUWERYS et al., 1985; NG et al., 1990; STENGEL et al., 1998);
- styrene (ASKERGREN et al., 1981a,b,c,d; FRANCHINI et al., 1983; LAUWERYS et al., 1985; VERPLANKE and HERBER, 1998; VIAU et al., 1987b; VYSKOCIL et al., 1989);
- methyl ethyl ketone (LAUWERYS et al., 1985);
- butoxyethanol (HAUFROID et al., 1997);
- ethylene glycol (GERIN et al., 1997);
- tetrachloroethene (FRANCHINI et al., 1983; LAUWERYS et al., 1983; 1985; MUTTI et al., 1992; PRICE et al., 1994, 1995; SOLET and ROBINS, 1991; VERPLANKE et al., 1999; VYSKOCIL et al., 1990);
- trichloroethene (BROGREN et al., 1986; NAGAYA et al., 1989; RASMUSSEN et al., 1993; SELDEN et al., 1993);
- 1,3-dichloropropene (BROUWER et al., 1991; OSTERLOH and FELDMAN, 1993);
- several organochlorine compounds (BOOGAARD et al., 1993; BOOGAARD and CAUBO, 1994).

Workplaces analysed included a rubber tire factory, shoe production, paint manufacturing, painting and spraying, oil refineries, printing, dry cleaning, reinforced



plastic industry, boat manufacturing, soil fumigation, and chemical companies (see Tab. 6.1).

### **Exposure assessment**

Most studies took great care in assessing past or current exposure: Past exposure was assessed by years of employment or years of exposure. In some studies, special exposure scores have been developed, which also considered different types of work (HOTZ et al., 1990, 1991, 1993, 1997; YAQOOB et al., 1993a,b) (see also Tab. 6.1). Recall bias may have occurred in the assessment of employment data, such as solvents used, number of tasks, and duration of the tasks. Current exposure was assessed by regular measurement of exposure concentrations at the workplaces and in some studies additionally by biomonitoring: determination of urinary metabolites in case of styrene (VERPLANKE and HERBER, 1998; VYSKOCIL et al., 1989), 2-but-oxyethanol (HAUFROID et al., 1997), toluene (NG et al., 1990), trichloroethene (BROGREN et al., 1986; NAGAYA et al., 1989; RASMUSSEN et al., 1993; SELDEN et al., 1993), and 1,3-dichloropropene (OSTERLOH et al., 1993); tetrachloroethene was determined in alveolar air (LAUWERYS et al., 1985; VERPLANKE et al., 1999) or in blood (LAUWERYS et al., 1983; MUTTI et al., 1992). Depending on the type of work, the controls may have been exposed as well. For example, in the study of ROCSKAY et al. (1993) the distinction between exposed and unexposed workers was "inside" or "outside" the calibration rooms. However, the workers outside the calibration rooms were more than negligibly exposed. Also, in the study of VIAU et al. (1987), some exposure of the controls to hydrocarbons has occurred with 0.2 to 2.1 mg/m<sup>3</sup>, as controls were from the same company with administrative or clerical functions.

### **Characterization of exposed workers**

Several studies lack information on physical characteristics of the study population, exclusion and inclusion criteria, consideration of potentially confounding variables such as alcohol, tobacco and analgesic consumption, exposure to known nephrotoxicants such as cadmium, lead and mercury. But there are also several studies available, where these factors have been analysed.

Usually only healthy workers were investigated. Workers with a story of kidney disease or risk factors for developing kidney disease such as increased protein excretion, diabetes mellitus, hypertension, chronic nephritis, renal stones, use of analgesics or possibly nephrotoxic drugs (diclofenac, ibuprofen) have been excluded from several studies (HOTZ et al., 1990; HOTZ, 1994; MEYER et al., 1984; MUTTI et al., 1992; NAGAYA et al., 1989; STENGEL et al., 1998; VERPLANKE and HERBER, 1998; VERPLANKE et al., 1999; VIAU et al., 1987; YAQOOB et al., 1993; ZSCHIESCHE and TRIEBIG, 1990).

### **Parameters measured**

Parameters which may be measured as biomarkers in urine to detect early functional alterations of the kidney have been presented in chapter 4.2. In the cross-sectional studies, many of these parameters have been measured, mostly albumin,  $\beta_2$ M, RBP and NAG (see Tab. 6.1). The most extensive analysis was carried out by MUTTI et

al. (1992), who in a European collaborative research project analysed more than 20 parameters in workers exposed to tetrachoroethene.

Urine samples were taken at different times and frequencies. E.g., spot urine, not further specified, was taken by SOLET and ROBINS (1991) and VIAU et al. (1987); overnight urine was used by FRANCHINI et al. (1983); VERPLANKE and HERBER (1998); and VERPLANKE et al. (1999); second morning urine by MUTTI et al. (1992); end-of-shift urine by VERPLANKE and HERBER (1998), VIAU et al. (1987); VYSKOCIL et al. (1990); and LAUWERYS et al. (1983); pre-shift and post-shift urine by VERPLANKE and HERBER (1998). More extended analyses included urine upon arrival at work and at the end of the work-shift on the first and last day of a typical work week (VIAU et al., 1987a,b; VYSKOCIL et al., 1989) or several samples during one workweek (VERPLANKE and HERBER, 1998; VERPLANKE et al., 1999).

In some studies, parameters were followed additionally (or only) over time (BROUWER et al., 1991; GERIN et al., 1997; OSTERLOH et al., 1993; ROCSKAY et al., 1993; STENGEL et al., 1998). Since the spectrum of parameters measured in these longitudinal observations was the same as in the cross-sectional ones, in this report the results of both are described and evaluated together.

Usually, differences in mean or median values between groups have been analysed. Some authors also analysed prevalence of abnormal values.

**Tab. 6.1** Overview of observed alterations<sup>1</sup> of biomarkers in studies on solvent-exposed workers (for abbreviations, see list in 9.2)

| Main compound | Parameter  |             |         |              |      |     |                  |                       |         |             |             |     |     |             | Reference |     |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                             |
|---------------|------------|-------------|---------|--------------|------|-----|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----------|-----|-------------|---------------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|-----|--|-----------------------------|
|               | In serum   |             |         |              |      |     |                  | In urine              |         |             |             |     |     |             |           |     |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                             |
|               | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal |           | AAP | $\beta$ Glu | Total protein | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD |  |                             |
| Styrene       |            |             |         |              |      |     |                  | -                     |         |             |             |     |     |             |           | -   | +           | +             |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  | FRANCHINI et al. (1983)     |
| Styrene       |            |             |         |              |      |     |                  | +                     |         |             |             | +   | -   | -           | -         |     |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  | VERPLANKE and HERBER (1998) |
| Styrene       |            |             |         |              |      |     |                  | +                     |         |             | -           |     |     |             |           |     |             |               | +        | +          |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | ASKERGREN et al. (1981a); ASKERGREN (1981) |                             |
| Styrene       |            |             |         |              |      |     |                  | +                     |         |             | -           |     |     |             |           |     |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | LAUWERYS et al. (1985)                     |                             |
| Styrene       |            |             |         |              |      |     |                  | -                     |         |             | -           |     |     |             |           |     |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | VIAU et al. (1987b)                        |                             |
| Styrene       |            |             |         |              |      |     |                  | -                     |         |             | -           |     | ?   |             |           |     |             |               | -        |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | VYSKOCIL et al. (1989)                     |                             |
| Toluene       |            |             |         |              |      |     |                  | ?                     |         |             |             | +   |     |             |           |     |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | NG et al. (1990)                           |                             |

| Main compound          | Parameter  |             |         |              |      |          |                  |                       |         |             |             |     |     |             |     |             |               | Reference |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                                |                       |
|------------------------|------------|-------------|---------|--------------|------|----------|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----|-------------|---------------|-----------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|-----|--------------------------------|-----------------------|
|                        | In serum   |             |         |              |      | In urine |                  |                       |         |             |             |     |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                                |                       |
|                        | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE      | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal | AAP | $\beta$ Glu | Total protein |           | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD |                                |                       |
| Toluene                | -          | -           |         | -            | -    | +        | -                | -                     | -       | -           | -           | -   | +   | -           | -   | -           | -             | -         | -        | -          | -            | -             | -   | -   | -    | -    | -   | -   | -                | -                | -                                   | -                                   | -   | -    | -   | -   | -   | -                              | STENGEL et al. (1998) |
| Toluene                |            |             |         |              |      |          |                  | ?                     |         |             | -           |     |     |             |     |             |               |           | +        | +          |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | ASKERGREN et al. (1981a,b,c,d) |                       |
| Xylene, toluene        |            |             |         |              |      |          |                  | ?                     |         | -           |             |     |     |             |     |             |               |           | +        | +          |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | ASKERGREN et al. (1981a,b,c,d) |                       |
| Toluene, xylene        |            |             |         |              |      |          |                  | -                     |         |             |             |     |     |             |     | +           | -             | ?         |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | FRANCHINI et al. (1983)        |                       |
| Toluene cont. solvents |            |             |         |              |      |          | -                | -                     |         | -           |             |     |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | KRUSELL et al. (1985)          |                       |
| White spirit, toluene  |            |             |         |              |      |          |                  | -                     |         | -           | -           | -   |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | LAUWERYS et al. (1985)         |                       |
| White spirit           |            |             |         |              |      |          |                  | -                     |         | -           | -           | -   |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | LAUWERYS et al. (1985)         |                       |
| Naphtha blends         | -          |             |         |              |      |          |                  | +                     |         |             |             |     |     |             |     |             |               |           | +        | +          | +            |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | HASHIMOTO et al. (1991)        |                       |

| Main compound                          | Parameter  |             |         |              |      |          |                  |                       |         |             |             |     |     |             |     |             |               | Reference |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       |                         |
|--|------------|-------------|---------|--------------|------|----------|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----|-------------|---------------|-----------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|-----|---|-----------------------|-------------------------|
|  | In serum   |             |         |              |      | In urine |                  |                       |         |             |             |     |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       |                         |
|  | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE      | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal | AAP | $\beta$ Glu | Total protein |           | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD |   |                       |                         |
| Naphtha blends                         |            |             |         |              |      |          | ?                |                       |         | -           |             | ?   |     |             |     |             | -             |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   | ROCSKAY et al. (1993) |                         |
| Petroleum naphtha                      |            |             |         |              |      |          |                  | -                     | -       | -           | -           | +   |     |             |     |             | -             |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | - |                       | VYSKOCIL et al. (1991)  |
| Aliphatic/ aromatic hc                 |            | -           |         | +            | ?    |          |                  | +                     |         | -           | -           | -   |     |             |     |             |               |           |          |            |              |               |     |     |      | +    |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       | VIAU et al. (1987)      |
| n-hexane                               |            |             |         |              |      |          |                  | -                     |         | -           | -           |     |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       | LAUWERYS et al. (1985)  |
| C <sub>5</sub> -C <sub>7</sub> alkanes |            |             |         |              |      |          |                  |                       |         |             |             |     |     |             |     |             | -             | +         |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       | FRANCHINI et al. (1983) |
| C <sub>5</sub> -C <sub>7</sub> alkanes |            | -           |         |              |      |          |                  | -                     |         |             |             |     |     |             |     |             | ?             | +         | ?        |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       | MUTTI et al. (1981)     |
| 2-butoxy-ethanol, MEK                  |            | -           |         |              |      |          |                  |                       |         |             |             | -   |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       | HAUFROID et al. (1997)  |
| MEK                                    |            |             |         |              |      |          |                  | -                     |         | -           | -           |     |     |             |     |             |               |           |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |   |                       | LAUWERYS et al. (1985)  |

| Main compound                | Parameter  |             |         |              |      |          |                  |                       |         |             |             |     |     |             |     | Reference |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |   |                                |
|------------------------------|------------|-------------|---------|--------------|------|----------|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----|-----------|-------------|---------------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|---|--------------------------------|
|                              | In serum   |             |         |              |      | In urine |                  |                       |         |             |             |     |     |             |     |           |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |   |                                |
|                              | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE      | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal | AAP |           | $\beta$ Glu | Total protein | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD   |                                |
| Paint solvents (painters)    |            |             |         |              |      |          |                  |                       |         | -           | -           | -   |     | +           |     | -         |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |   | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents (sprayers)    |            |             |         |              |      |          |                  |                       |         |             |             | +   |     | -           |     | +         |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |   | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents               | ?          |             |         |              |      |          |                  | -                     | -       |             | -           | ?   |     |             |     | ?         |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     | YAQOOB et al. (1993), PAI et al. (1996, 1998) |                                |
| Paint solvents               |            |             | ?       | +            | ?    |          |                  |                       |         |             |             |     |     |             |     |           |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     | STEVENSON et al. (1995)                       |                                |
| Petroleum-based mineral oils |            |             | +       | ?            | +    |          |                  |                       |         |             |             |     |     |             |     |           |             |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     | STEVENSON et al. (1995)                       |                                |

| Main compound                | Parameter  |             |         |              |      |     |                  |                       |         |             |             |     |     |             |     |             | Reference |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                         |   |
|------------------------------|------------|-------------|---------|--------------|------|-----|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----|-------------|-----------|---------------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|-----|-------------------------|---|
|                              | In serum   |             |         |              |      |     | In urine         |                       |         |             |             |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                         |   |
|                              | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal | AAP | $\beta$ Glu |           | Total protein | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD |                         |   |
| Petroleum-based mineral oils | ?          |             |         |              |      |     | -                | ?                     |         |             | ?           | ?   |     |             |     |             | ?         |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                         | YAQOOB et al. (1993), PAI et al. (1996, 1998) |
| Hydrocarbon mixtures         |            |             |         |              |      |     | -                |                       |         |             | -           |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                         | HOTZ et al. (1997)                            |
| (Refinery workers)           |            |             |         |              |      |     | -                | ?                     |         |             |             | -   |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                         | + GRUENER (1992)                              |
| (Various)                    | -          |             |         |              |      |     | ?                |                       |         |             |             | +   |     |             |     |             | -         |               |          |            | +            |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | HOTZ et al. (1989)      |   |
| (Various)                    | ?          |             | +       |              |      |     | +                |                       |         | ?           |             | +   |     |             |     |             |           |               |          |            | ?            |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |                         | HOTZ et al. (1990, 1993)                      |
| (Various)                    |            |             |         |              |      |     |                  |                       |         |             |             | +   |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | MEYER et al. (1984)     |   |
| Tetrachloroethene            |            |             |         |              |      |     | -                |                       |         |             |             |     |     |             |     | +           | -         | +             |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     | FRANCHINI et al. (1983) |   |

| Main compound      | Parameter  |             |         |              |      |     |                  |                       |         |             |             |     |     |             |     |             | Reference |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        |                         |                              |
|--------------------|------------|-------------|---------|--------------|------|-----|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----|-------------|-----------|---------------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|------------------------|-------------------------|------------------------------|
|                    | In serum   |             |         |              |      |     | In urine         |                       |         |             |             |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        |                         |                              |
|                    | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal | AAP | $\beta$ Glu |           | Total protein | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD                    |                         |                              |
| Tetrachloro-ethene | -          | -           |         |              |      |     |                  | -                     |         | -           | -           |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        |                         | LAUWERYS et al. (1983, 1985) |
| Tetrachloro-ethene | -          | -           | +       |              | +    |     |                  | +                     | +       | ?           | ?           | -   |     |             |     |             | -         |               |          |            |              | ?             | +   | +   | +    | +    | +   | -   | -                | -                | -                                   |                                     | +   | +    |     |     | MUTTI et al. (1992)    |                         |                              |
| Tetrachloro-ethene |            |             | +       |              |      |     |                  |                       |         |             |             |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        | PRICE et al. (1994)     |                              |
| Tetrachloro-ethene |            |             | +       |              |      |     |                  |                       |         |             |             |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        | PRICE et al. (1995)     |                              |
| Tetrachloro-ethene |            |             |         |              |      |     |                  | -                     |         |             |             | -   |     |             |     |             | -         |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        | SOLET and ROBINS (1991) |                              |
| Tetrachloro-ethene |            |             |         |              |      |     |                  | -                     |         |             | +           | -   | -   | -           |     |             | -         |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |                        | VERPLANKE et al. (1999) |                              |
| Tetrachloro-ethene |            |             |         |              |      |     |                  | -                     |         | -           |             |     |     |             |     |             | ?         | +             |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      | -   |     | VYSKOCIL et al. (1990) |                         |                              |
| Trichloro-ethene   |            |             |         |              |      |     |                  |                       |         | -           |             |     |     |             |     |             | ?         |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     | NAGAYA et al. (1989)   |                         |                              |



| Main compound            | Parameter  |             |         |              |      |     |                  |                       |         |             |             |     |     |             |     |             | Reference |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                       |                           |
|--------------------------|------------|-------------|---------|--------------|------|-----|------------------|-----------------------|---------|-------------|-------------|-----|-----|-------------|-----|-------------|-----------|---------------|----------|------------|--------------|---------------|-----|-----|------|------|-----|-----|------------------|------------------|-------------------------------------|-------------------------------------|-----|------|-----|-----|-----|--|-----------------------|---------------------------|
|                          | In serum   |             |         |              |      |     | In urine         |                       |         |             |             |     |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                       |                           |
|                          | Creatinine | $\beta_2$ M | Laminin | Anti-Laminin | AGBM | IgE | Creat. clearance | $\beta_2$ M clearance | Albumin | Transferrin | $\beta_2$ M | RBP | NAG | $\beta$ Gal | AAP | $\beta$ Glu |           | Total protein | Lysozyme | Leucocytes | Erythrocytes | Cell sediment | IgG | THG | GAGs | BB50 | HF5 | BBA | PGE <sub>2</sub> | TXB <sub>2</sub> | PGF <sub>1<math>\alpha</math></sub> | PGF <sub>2<math>\alpha</math></sub> | IAP | TNAP | FNU | LDH | SOD |  |                       |                           |
| Trichloroethene          |            |             |         |              |      |     |                  |                       |         |             |             | +   |     |             |     |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  | BROGREN et al. (1986) |                           |
| Several organochlorines* |            |             |         |              |      |     |                  | +                     |         |             |             | -   |     |             | -   |             | -         |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                       | BOOGAARD et al. (1993)    |
| Several organochlorines* | -          |             |         |              |      |     |                  | ?                     |         |             | -           |     | -   |             | -   |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                       | BOOGAARD and CAUBO (1994) |
| 1,3-DCP                  | -          | -           |         |              |      |     |                  | +                     |         |             | -           | +   |     | -           | -   |             |           |               |          |            |              |               |     |     |      |      |     |     |                  |                  |                                     |                                     |     |      |     |     |     |  |                       | BROUWER et al. (1991)     |

\*: allyl chloride, epichlorhydrin, 1,3-dichloropropene, hexachlorocyclopentadiene

1: +: effect observed (e.g. significantly increased protein excretion or enzyme activity in urine);

?: possible effect (e.g. non-significant increase, no exposure-response-relationship, non-consistent pattern of alterations);

-: no effect observed

### 6.3.2 Results

Numerical values of the parameters measured are listed in Tab. 9.1 to Tab. 9.10 in the annex. The parameters where any kind of changes occurred are summarized in Tab. 6.1. As can be seen from Tab. 6.1, in several studies some of the parameters were altered, either means or medians being elevated significantly in the solvent-exposed group compared to control. A higher (although only in some studies statistically significant) prevalence of abnormal values was found in several studies (MUTTI et al., 1992; STEVENSON et al., 1995; VIAU et al., 1997, VYSKOCIL et al., 1987, 1990, 1991).

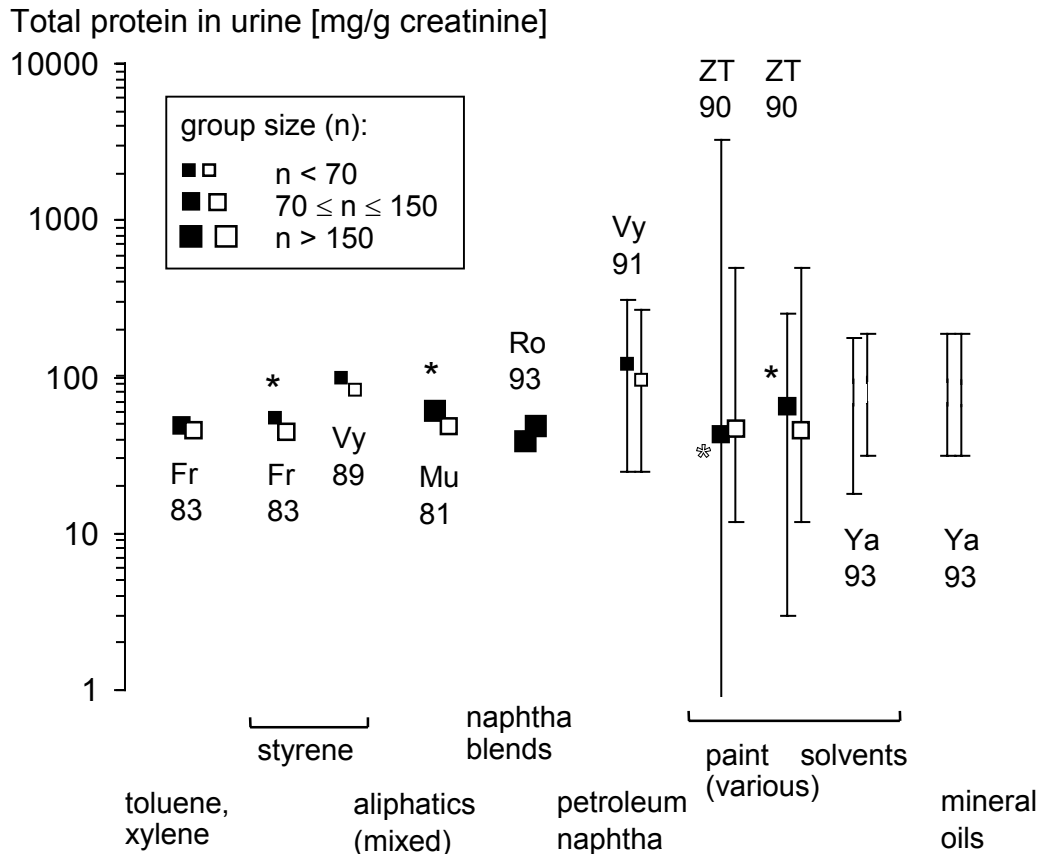
In the following, the outcome of the cross-sectional studies are analysed according to the parameters that were measured in the individual studies. Background information to these parameters can be found in the correspondingly numbered chapters 4.2.1 to 4.2.13. A few further parameters have not been included here since they are not well defined, are only rarely measured in single studies together with other, more elaborated parameters, and are unlikely to add additional information to the results obtained from the other parameters. They are, however, included in the description of results in Tab. 6.1).

#### 6.3.2.1 Total protein

The values of total protein in urine of solvent-exposed and control workers are compiled in Tab. 9.7, and the results are summarized in Tab. 6.1, Fig. 6.1 and Fig. 6.2.

Similar to albumin (see Fig. 6.1 to Fig. 6.3 below), in several studies slightly increased concentrations of total protein in urine have been found. A higher range for exposed than for unexposed workers was observed in the study of VERPLANKE et al (1999), and, less pronounced, in the study of VYSKOCIL et al. (1990). Both were conducted on tetrachloroethene-exposed workers.

Furthermore, HASHIMOTO et al. (1991) observed that a positive reaction for urinary protein determined with test strips (mainly reacting to albumin) only occurred in a number of samples from naphtha exposed press workers, but in none of the controls.



**Fig. 6.1** Comparison of total protein concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) - part I, continued in Fig. 6.2. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies (full asterisks indicate significant elevation; in the study of ZSCHIESCHE and TRIEBIG, 1990, significantly lower values were noted for the exposed workers). Abbreviations of study authors: Fr83: FRANCHINI et al. (1983); Vy89: VYSKOCIL et al. (1989); Mu81: MUTTI et al. (1981); Ro93: ROCSKAY et al. (1993); Vy91: VYSKOCIL et al. (1991); ZT90: ZSCHIESCHE and TRIEBIG (1990); Ya93: YAQOOB et al. (1993). Cf. Tab. 9.7.

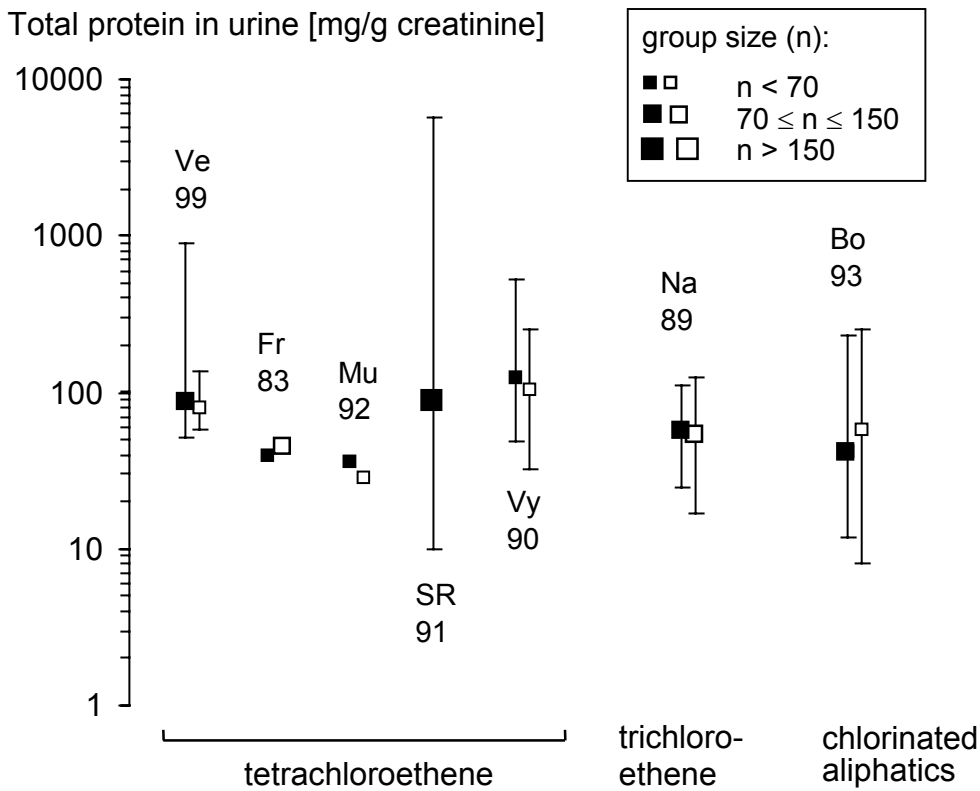


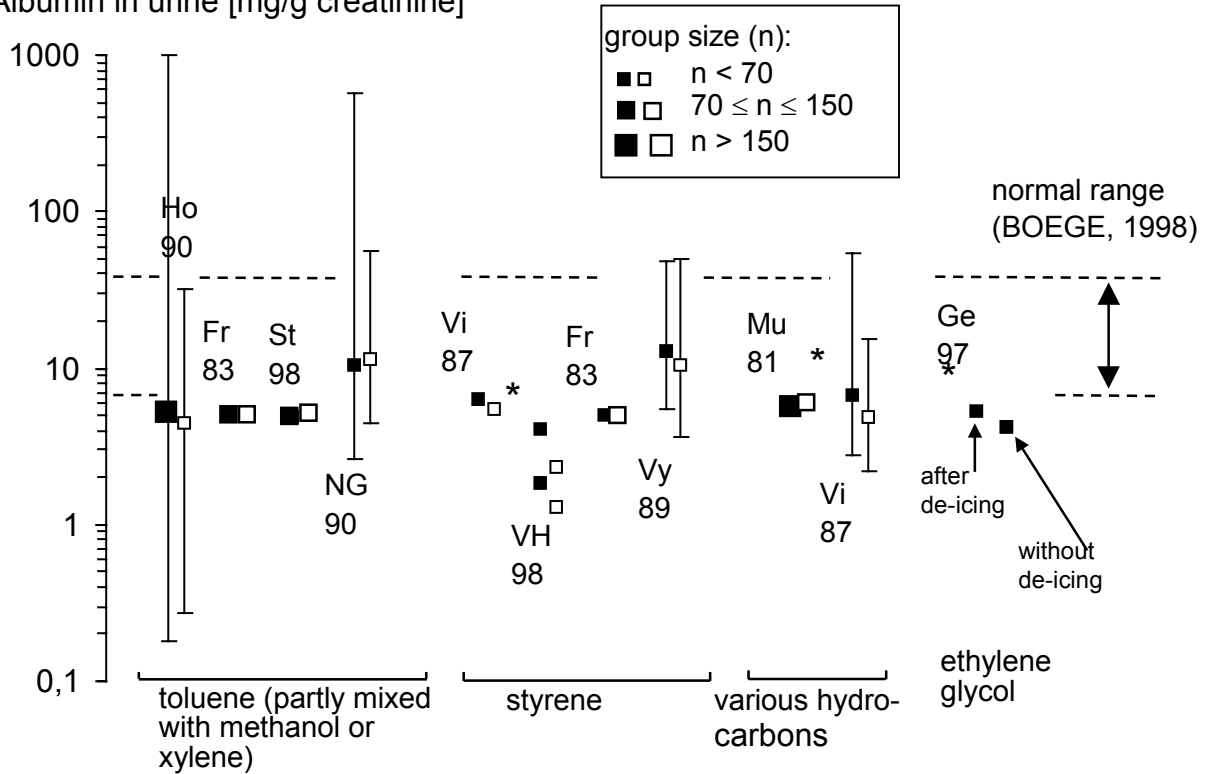
Fig. 6.2

Comparison of total protein concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) - part II, continued from Fig. 6.1. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. The sequence of studies with tetrachloroethene is arranged according to TWA exposure concentration (in ascending order). Abbreviations of study authors: Ve99: VERPLANKE et al. (1999); Fr83: FRANCHINI et al. (1983); Mu92: MUTTI et al. (1992); SR91: SOLET and ROBINS (1991); Vy90: VYSKOCIL et al. (1990); Na89: NAGAYA et al. (1989); Bo93: BOOGAARD et al. (1993). Cf. Tab. 9.7.

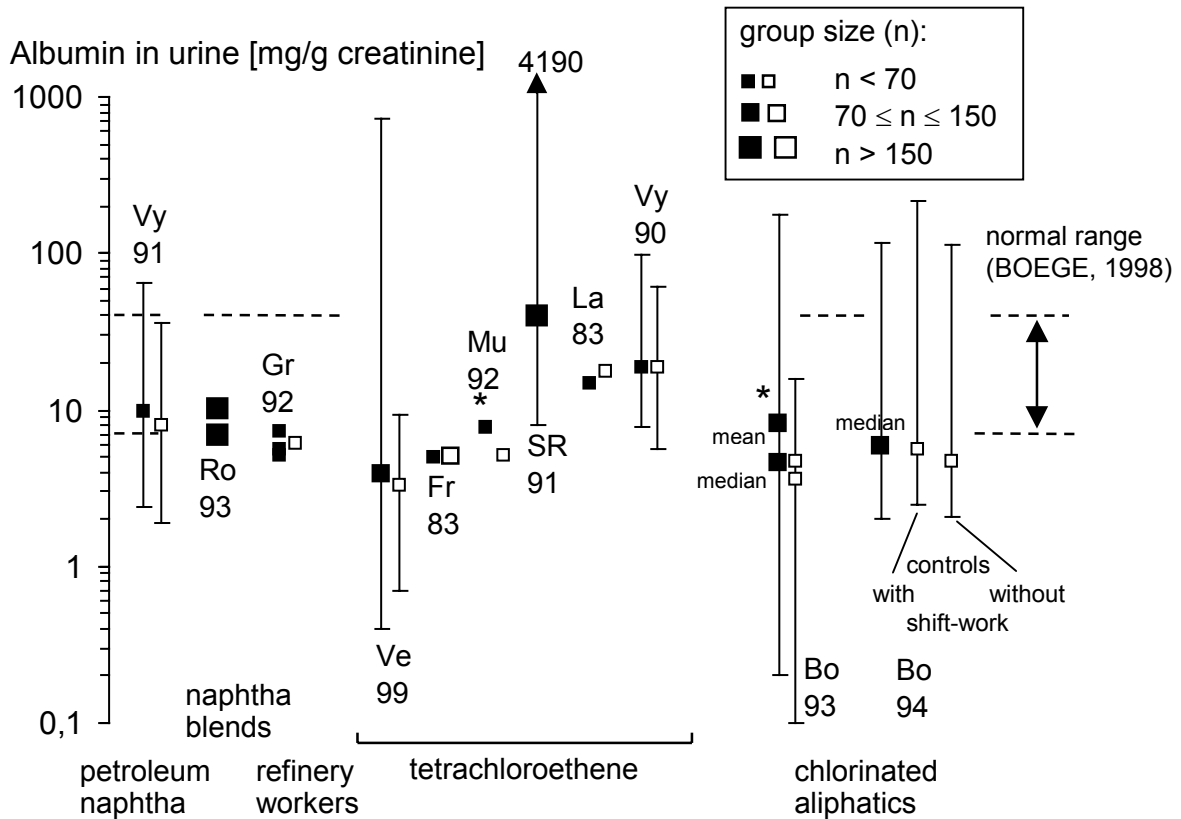
6.3.2.2 Albumin

Albumin is the protein which has been assayed most frequently in the studies. The values of albumin in urine of solvent-exposed and control workers are compiled in Tab. 9.1, Tab. 6.1, and in Fig. 6.1 to Fig. 6.3.

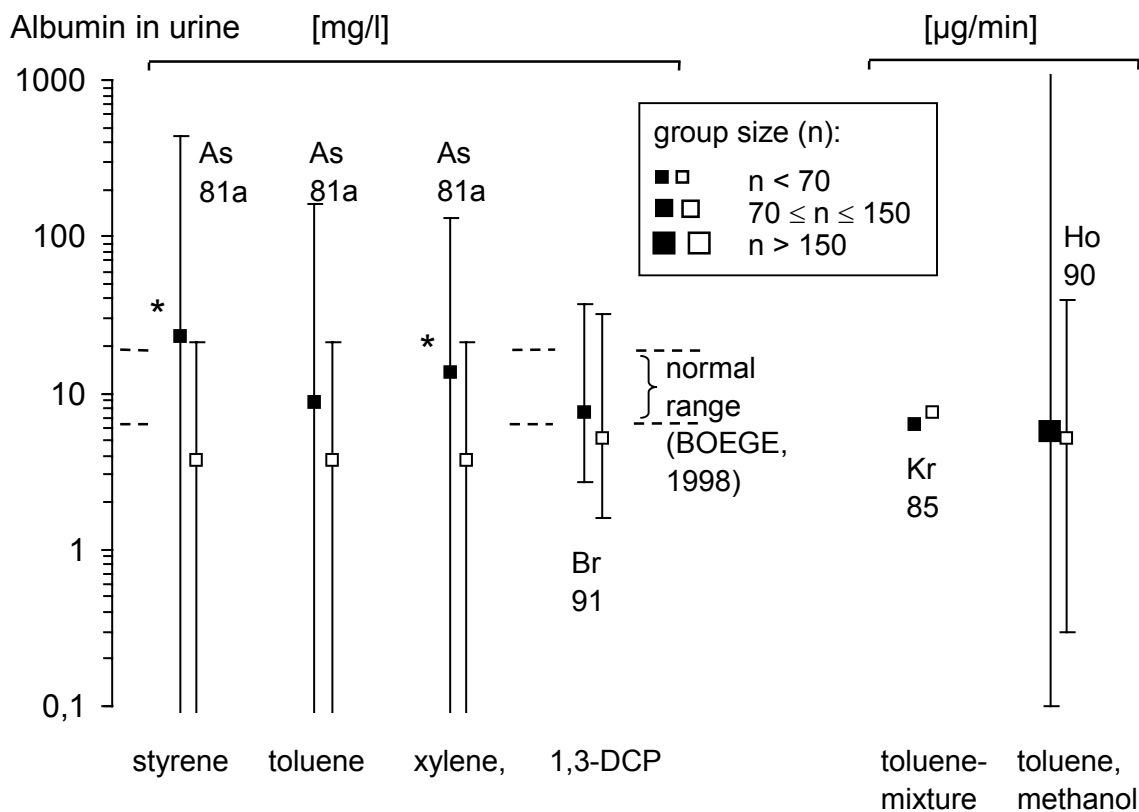
Albumin in urine [mg/g creatinine]



**Fig. 6.1** Comparison of albumin concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part I, continued in Fig. 6.2 and Fig. 6.3. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies. The sequence of studies within the blocks of substances is arranged according to exposure concentration (in ascending order). Abbreviations of study authors: Ho90: HOTZ et al. (1990); Fr83: FRANCHINI et al. (1983); St98: STENGEL et al. (1998); Vi87: VIAU et al. (1987); Ng90: NG et al. (1990); VH98: VERPLANKE and HERBER (1998); Vy89: VYSKOCIL et al. (1989); Mu81: MUTTI et al. (1981); Vi87: VIAU et al. (1987); Ge97: GERIN et al. (1997). Cf. Tab. 9.1, for normal range, see Tab. 4.1.



**Fig. 6.2** Comparison of albumin concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part II, continued from Fig. 6.1. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies. The sequence of studies with tetrachloroethene exposure is arranged according to TWA exposure concentration (in ascending order). Abbreviations of study authors: Vy91: VYSKOCIL et al. (1991); Ve99: VERPLANKE et al. (1999); Fr83: FRANCHINI et al. (1983); Mu92: MUTTI et al. (1992); SR91: SOLET and ROBINS (1991); La83: LAUWERYS et al. (1983); Vy90: VYSKOCIL et al. (1990); Bo93: Boogard et al. (1993); BOOGAARD and CAUBO (1994). Cf. Tab. 9.1, for normal range, see Tab. 4.1.



**Fig. 6.3** Comparison of albumin concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part III, continued from Fig. 6.1 and Fig. 6.2. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies. Abbreviations of study authors: As81a: ASKERGREN et al. (1981a); Br91: BROUWER et al. (1991); Kr85: KRUSELL et al. (1985); Ho90: HOTZ et al. (1990). Cf. Tab. 9.1, for normal range, see Tab. 4.1.

Most studies noted differences between the mean or median albumin excretion in urine of workers exposed to solvents and controls; in several studies, the differences were statistically significant (ASKERGREN et al., 1981a; BOOGAARD et al., 1993; BOOGAARD and CAUBO, 1994; BROUWER et al., 1991; HASHIMOTO et al., 1991; HOTZ et al., 1990; MUTTI et al., 1992; NORMAND et al., 1989, 1990; VERPLANKE and HERBER, 1998; VIAU et al., 1987). Also, frequently the range of the values or the standard deviation was higher in workers than in controls and was also higher than the range considered as normal (BOEGE, 1998), indicating increases in individual workers (see Tab. 6.1 and Tab. 6.2).

Furthermore, HASHIMOTO et al. (1991) observed that a positive reaction for urinary protein determined with test strips (mainly reacting to albumin) only occurred in a number of samples from naphtha exposed press workers, but in none of the controls. In a study of workers exposed to toluene, STENGEL et al. (1998) found no changes in mean values of albumin excretion after two years. Also, comparison of albumin excretion in a subgroup of initially 18 newly employed workers before and after 1 and

3 years of exposure revealed no changes in mean albumin excretion. However, the data after 3 years comprise only 15 measurements and no explanation is given for the missing values.

In the study of SOLET and ROBINS (1991) the mean albumin value in the exposed group was the highest of all studies. No controls were investigated. The detection limit for the analysis of albumin was rather high, and therefore, no real measured values were available for 31 % of the study population. The calculation of mean values for these samples was carried out assuming half of the detection limit, 2.5 mg/g creatinine. It is not clear how realistic the mean is. Nevertheless, in this study also the highest albumin concentration in the urine was found.

#### 6.3.2.3 Transferrin

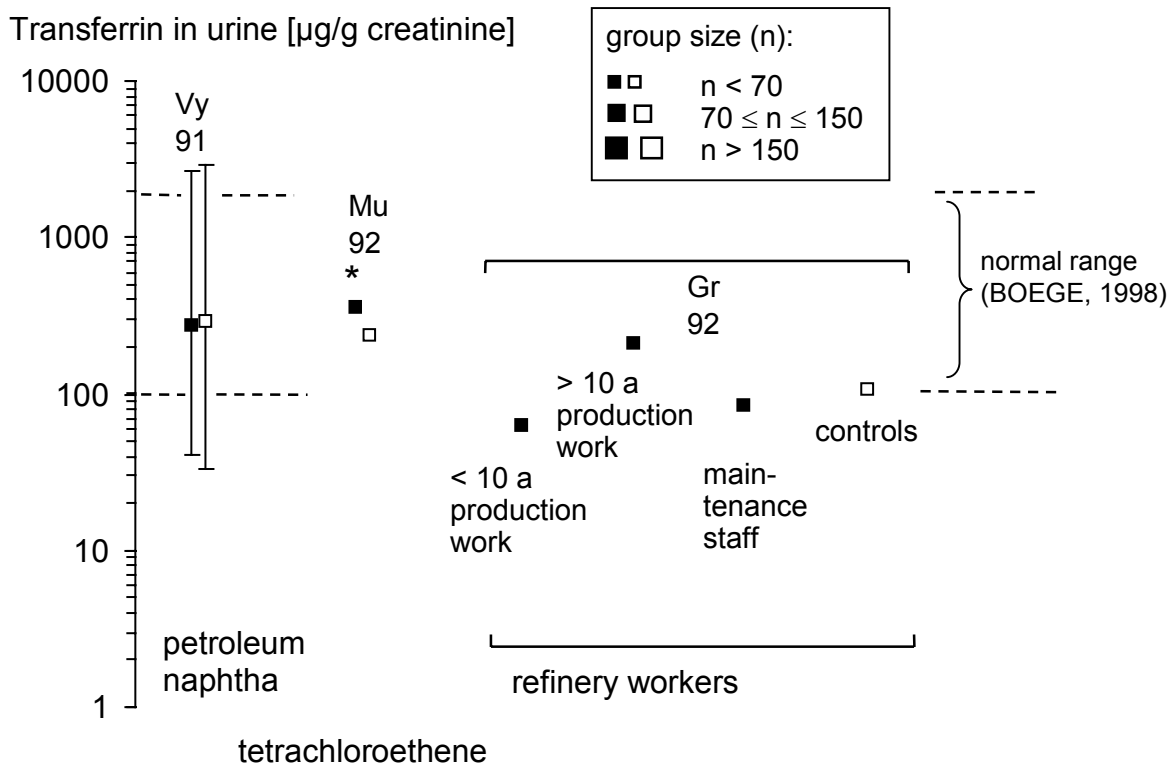
The values of transferrin in urine of solvent-exposed and control workers are compiled in Tab. 9.9, and the results are summarized in Tab. 6.1 and Fig. 6.1.

GRUENER (1992) found a significant increase in transferrin levels in urines of the refinery production workers who had worked more than 10 years. Also the number of workers who showed levels above the 97.5 percentile of the control group was increased. In the same study albumin levels were not significantly increased, thus supporting the view that transferrin may be a more sensitive marker also in solvent-exposed workers. In the study of MUTTI et al. (1992), both parameters were increased after exposure to tetrachloroethene, while VYSKOCIL et al. (1991) found no increase in both parameters in workers exposed to petroleum naphtha.

#### 6.3.2.4 IgG

Data for IgG are presented only in the study of MUTTI et al. (1992) on tetrachloroethene exposed workers. In that study, the mean IgG excretion in urine was not different between exposed and control group, but abnormally high values occurred significantly higher in the exposed group of workers.





**Fig. 6.1** Comparison of transferrin concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols). The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisk indicates statistically significant difference according to the authors of the study. Abbreviations of study authors: Vy91: VYSKOCIL et al. (1991); Mu92: MUTTI et al. (1992); Gr92: GRUENER (1992). Cf. Tab. 9.9, for normal range, see Tab. 4.1.

#### 6.3.2.5 $\beta_2$ -Microglobulin

$\beta_2$ -microglobulin ( $\beta_2\text{M}$ ) has been assayed in a number of the cross-sectional studies (Tab. 6.1). The values of  $\beta_2\text{M}$  in urine of solvent-exposed and control workers are compiled in Tab. 9.2 and are shown in Fig. 6.1 and Fig. 6.2.

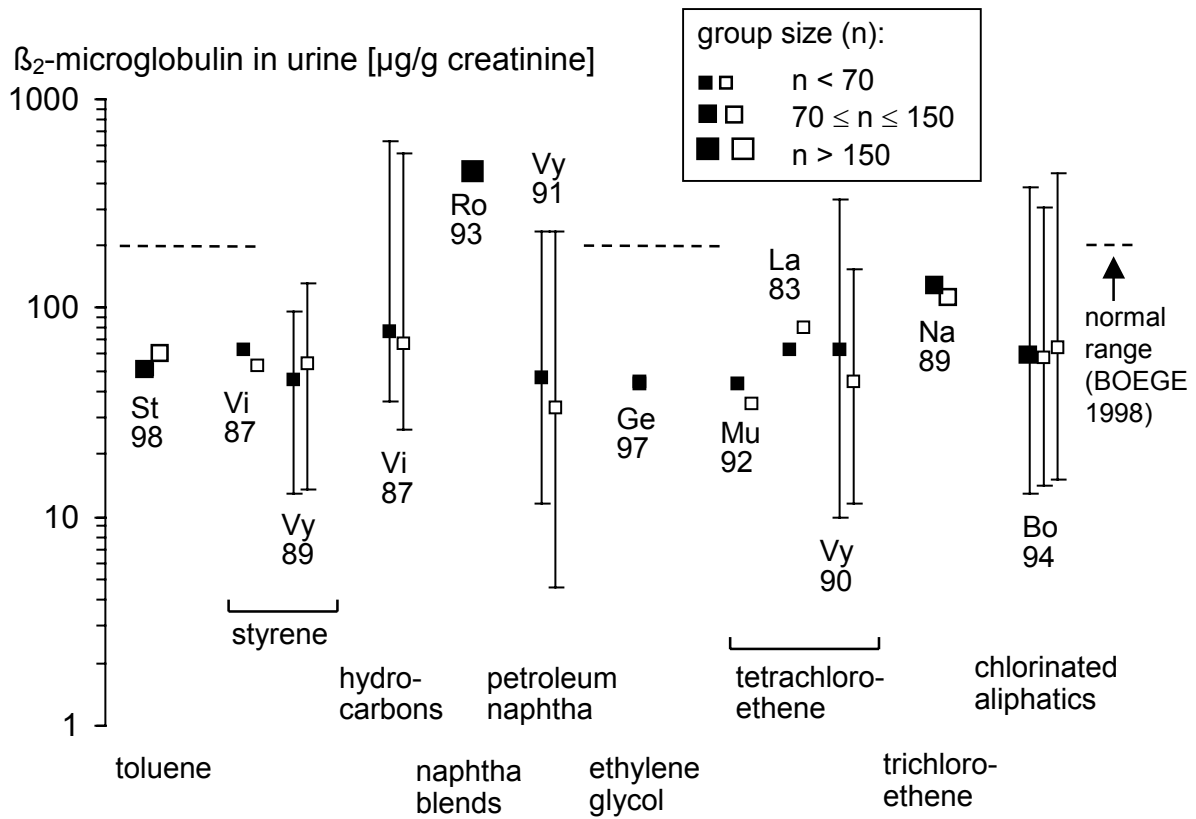
None of the studies found a significant increase of the mean  $\beta_2\text{M}$  excretion in solvent-exposed workers. Moreover, only one study reported a higher prevalence of abnormally high values in exposed workers (MUTTI et al., 1992).

Excretion of  $\beta_2\text{M}$  is regarded as a very sensitive parameter to indicate renal tubular damage. Therefore, the results described could suggest that the tubulotoxic potential of solvent exposure was low in the studies where  $\beta_2\text{M}$  was measured. This suggestion is supported by the observation that the excretion of RBP (see below, Fig. 6.1), which indicates similar damage and is of similar sensitivity, also was not increased in those studies in which both parameters were measured (LAUWERYS et al., 1983; VIAU et al., 1987; VYSKOCIL et al., 1989, 1991).

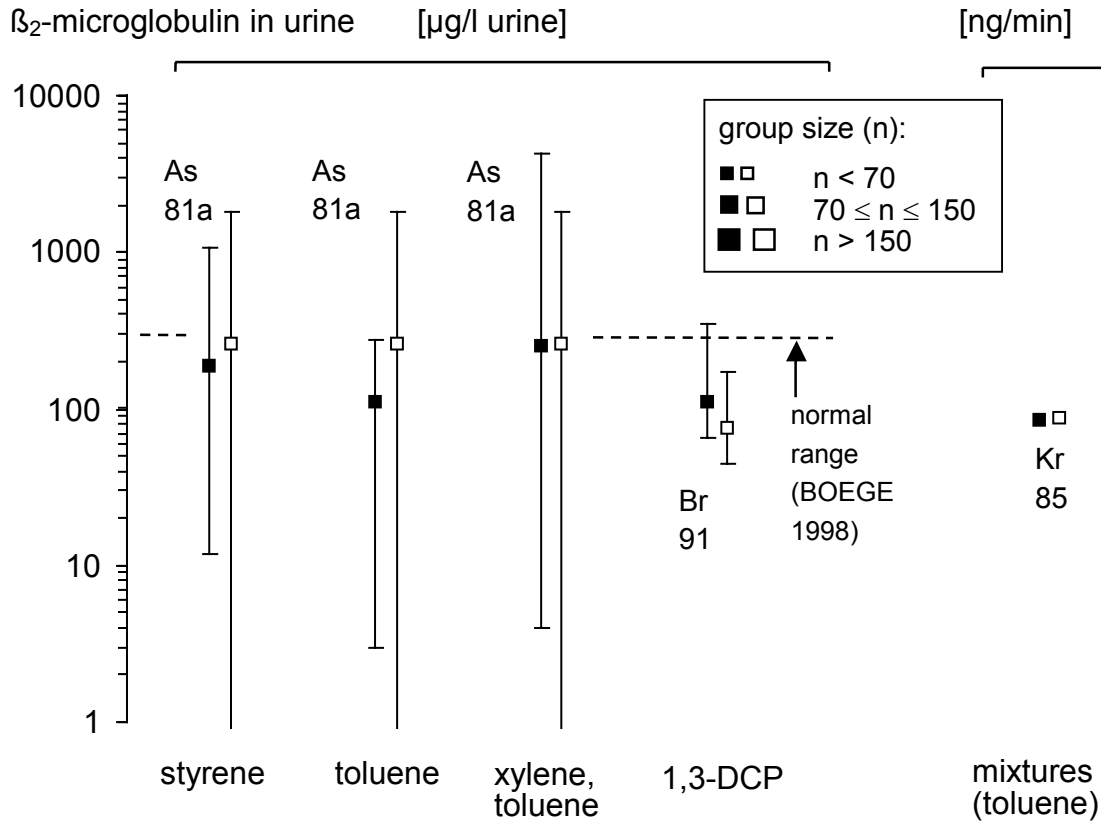
Results may also be compared with those obtained for NAG-activity in urine (see below, Fig. 6.1 and Fig. 6.2). In three studies, both  $\beta_2$ M and NAG were measured. An increased NAG-activity in urine of solvent-exposed workers was found in the studies of VYSKOCIL et al. (1989, 1991), no increase was observed by MUTTI et al. (1992).

NAG is a marker of renal tubular injury, which, however seems to be less sensitive than  $\beta_2$ -microglobulin or RBP. Thus, no increase in  $\beta_2$ M excretion and a concomitantly increased NAG-activity in the same group of workers is a puzzling result which is not readily explicable. However, although both are markers of tubular dysfunction, they do not indicate strictly the same damage: While an increase of  $\beta_2$ M in urine indicates a reduced tubular reabsorption ability, an increased NAG-activity indicates an enhanced release of this lysosomal enzyme from tubular cells.

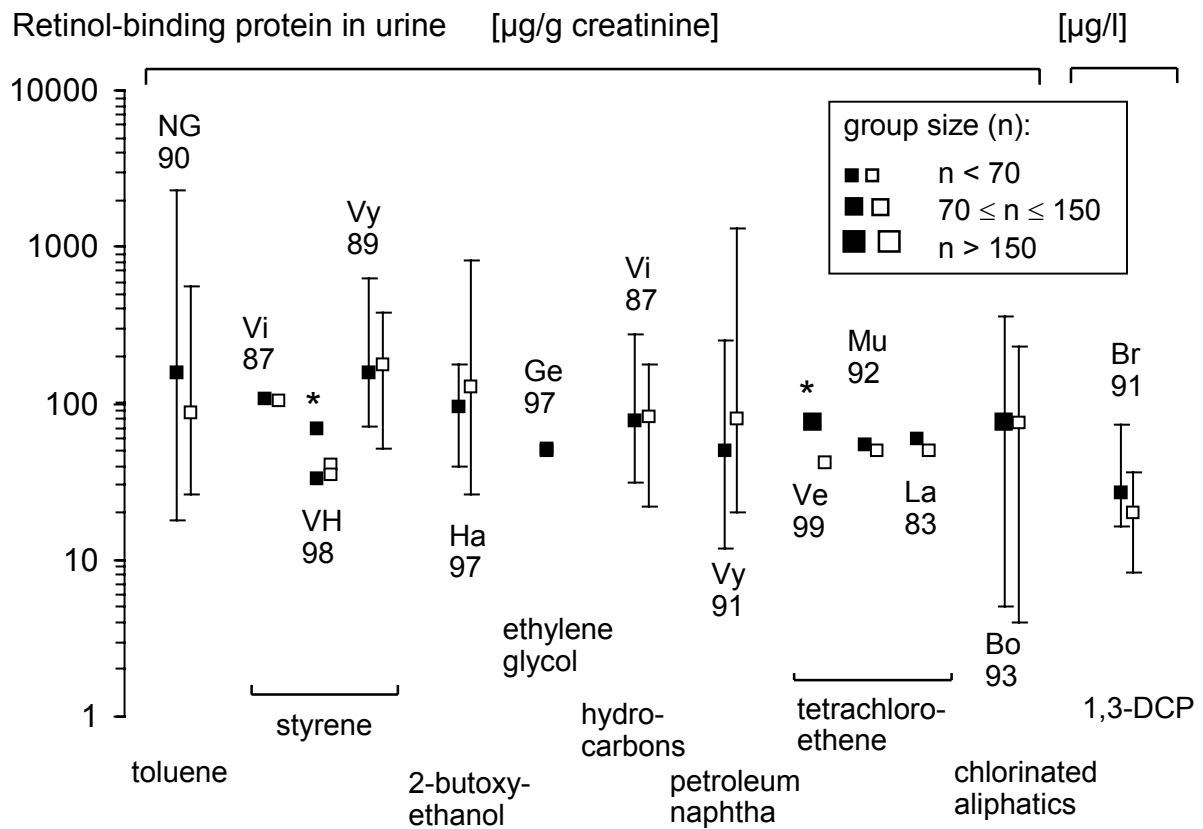
It may also be argued that the well-known acid-lability of  $\beta_2$ M could have led to a destruction of the enzyme in urine before the sample could be analysed. If this is true, it should be reflected by low mean values. However, as can be seen from Fig. 6.1 and Fig. 6.2, the reported values in many studies are not exceedingly low, but are in the normal ranges reported (see Tab. 4.2) or even at the upper end of the normal range for healthy individuals. Therefore, it is unlikely that degradation of  $\beta_2$ M influenced the outcome of the studies presented here..



**Fig. 6.1** Comparison of  $\beta_2$ -microglobulin ( $\beta_2$ M) concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part I, continued in Fig. 6.2. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. The sequence of studies with tetrachloroethene exposure is arranged according to TWA exposure concentration (in ascending order). The data point for the study of GERIN et al. (1997) is composed of two squares – almost completely molten together – for two sampling periods: end-of-shift-values after de-icing and in period without de-icing, respectively (cf. Fig. 6.1). Abbreviations of study authors: St98: STENGEL et al. (1998); Vy89: VYSKOCIL et al. (1989); Vi87: VIAU et al. (1987); Ro93: ROCSKAY et al. (1993); Vy91: VYSKOCIL et al. (1991); Ge97: GERIN et al. (1997); Mu92: MUTTI et al. (1992); La83: LAUWERYS et al. (1983); Vy90: VYSKOCIL et al. (1990); NAGAYA et al. (1989); Bo94: Boogard and CAUBO (1994). Cf. Tab. 9.2, for normal range, see Tab. 4.1.



**Fig. 6.2** Comparison of  $\beta_2$ -microglobulin ( $\beta_2$ M) concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part II, continued from Fig. 6.1. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Abbreviations of study authors: As81a: ASKERGREN et al. (1981a); Br91: BROUWER et al. (1991); Kr85: KRUSELL et al. (1985). Cf. Tab. 9.2, for normal range, see Tab. 4.1.

6.3.2.6 Retinol-binding protein

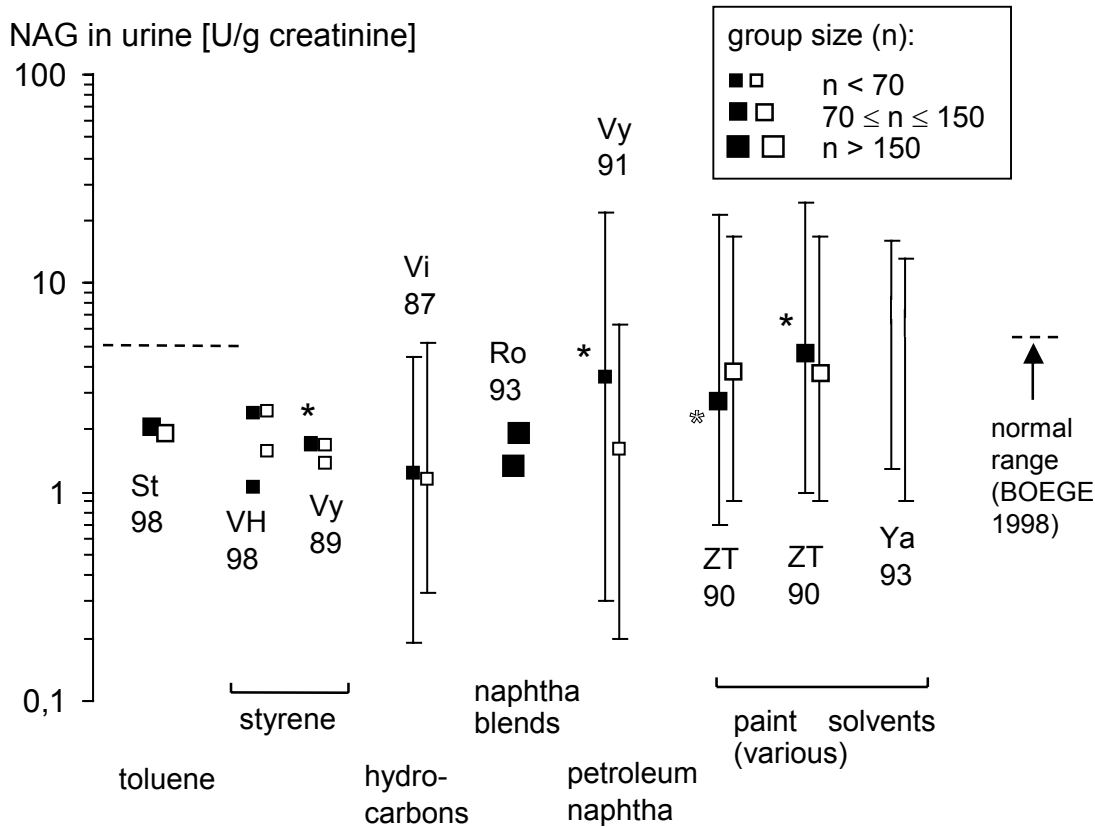
**Fig. 6.1** Comparison of retinol-binding protein (RBP) concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols). The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies. The sequence of studies within the blocks of substances (styrene and tetrachloroethene) is arranged according to exposure concentration (in ascending order). The data point for the study of GERIN et al. (1997) is composed of two squares – almost completely molten together – for two sampling periods: end-of-shift-values after de-icing and in period without de-icing, respectively (cf. Fig. 6.1). Abbreviations of study authors: Ng90: NG et al. (1990); VH98: VERPLANKE and HERBER (1998); Vy89: VYSKOCIL et al. (1989); Ha97: HAUFROID et al. (1997); Ge97: GERIN et al. (1997); Vi87: VIAU et al. (1987); Vy91: VYSKOCIL et al. (1991); Ve99: VERPLANKE et al. (1999); Mu92: MUTTI et al. (1992); La83: LAUWERYS et al. (1983); Bo93: Boogard et al. (1993); Br91: BROUWER et al. (1991). Cf. Tab. 9.3.

Retinol-binding protein (RBP) is considered to be a very sensitive parameter of tubular dysfunction for which a higher sensitivity than for NAG was reported (BERNARD et al., 1987). However, it was increased in rather few cross-sectional studies (BROUWER et al., 1991; NG et al., 1990; MUTTI et al., 1992; NORMAND et

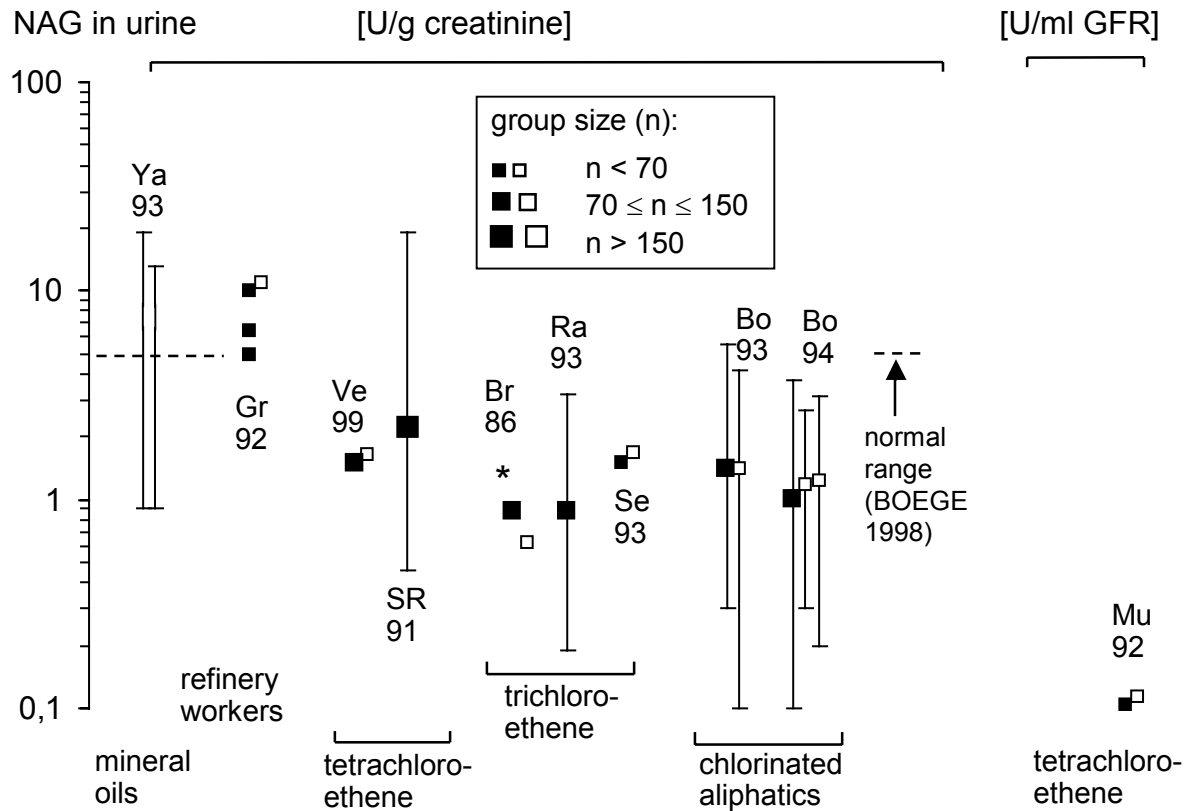
al., 1989, 1990; VERPLANKE and HERBER, 1998; VERPLANKE et al., 1999; YAQOOB et al., 1983; 1993) (see Tab. 9.3, Tab. 6.1, and Fig. 6.1).

### 6.3.2.7 N-acetyl- $\beta$ -D-glucosaminidase

The values of N-Acetyl- $\beta$ -D-glucosaminidase (NAG) in urine of exposed and control workers in the cross-sectional studies on solvent exposure are compiled in Tab. 9.4 and are shown in Fig. 6.1 and Fig. 6.2.

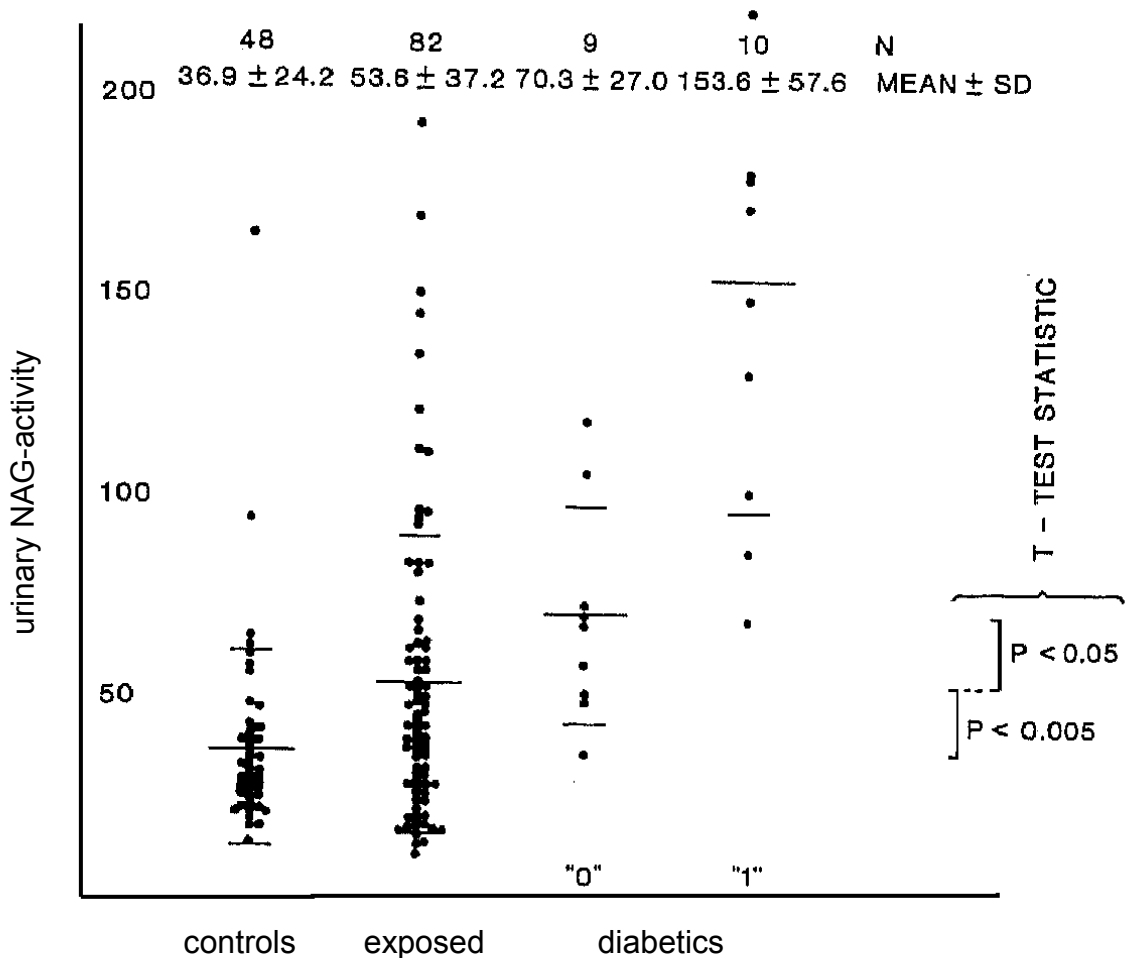


**Fig. 6.1** Comparison of N-acetyl- $\beta$ -D-glucosaminidase (NAG) activity in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part I, continued in Fig. 6.2. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies (full asterisks indicate significant elevation; in the study of ZSCHIESCHE and TRIEBIG, 1990, significantly lower values were noted for the exposed workers). Abbreviations of study authors: St98: STENDEL et al. (1998); VH98: VERPLANKE and HERBER (1998); Vy89: VYSKOCIL et al. (1989); Vi87: VIAU et al. (1987); Ro93: ROCSKAY et al. (1993); Vy91: VYSKOCIL et al. (1991); ZT90: ZSCHIESCHE and TRIEBIG (1990); Ya93: YAQOOB et al. (1993). Cf. Tab. 9.4, for normal range, see Tab. 4.1.



**Fig. 6.2** Comparison of N-acetyl- $\beta$ -D-glucosaminidase (NAG) activity in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols) – part II, continued from Fig. 6.1. The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. The study of BOOGAARD and CAUBO (1994) contains two control groups: with (left) and without (right) shift-work, respectively (cf. Fig. 6.2). Asterisk indicates statistically significant difference according to the authors of the study. Abbreviations of study authors: Ya93: YAQOOB et al. (1993); Gr92: GRUENER (1992); Ve99: VERPLANKE et al. (1999); SR91: Solet and Robins (1991); Br86: BROGREN et al. (1986); Ra93: RASMUSSEN et al. (1993); SELDEN et al. (1993); Bo93: BOOGAARD et al. (1993); Bo94: BOOGAARD and CAUBO (1994); Mu92: MUTTI et al. (1992). Cf. Tab. 9.4, for normal range, see Tab. 4.1.

NAG has been analysed in a great number of cross-sectional studies and a statistically significant increase was found in several of them (Tab. 6.1) (HOTZ et al., 1989, 1990; MEYER et al., 1984; NORMAND et al., 1989, 1990; PAI et al., 1996, 1998; STENGEL et al., 1998; VYSKOCIL et al., 1989, 1991; YAQOOB et al., 1983; 1993; ZSCHIESCHE and TRIEBIG, 1990).



**Fig. 6.3** Urinary NAG-excretion in metal industry workers exposed to chlorinated organic solvents (largely trichloroethene) compared to unexposed workers (controls) and diabetic patients without ("0") or with ("1") diabetic subclinical nephropathy (as diagnosed by increased albumin excretion). NAG-activity is expressed as  $\mu\text{mol}$  4-methylumbelliferone released/(h · g creatinine). Diagram from BROGREN et al. (1986).

As an example, the results of the study of BROGREN et al. (1986) on trichloroethene-exposed workers are shown in Fig. 6.3. The presentation of individual test results as dots shows the distribution of values with some measurements in the exposed group outside the normal range of non-exposed workers. Furthermore, it can be seen that the NAG-activity in urine of some exposed workers is as high as in diabetic patients with subclinical diabetic nephropathy (diagnosed by increased albumin excretion). Unfortunately, albumin excretion in workers was not determined in that study so that their renal status cannot be further evaluated.

In the study of GRUENER (1992), NAG values were rather high, compared to other studies. But also the reported reference values of the investigating laboratory exceed the values given by other authors nearly tenfold. Possibly, this is due to the method of analysis.

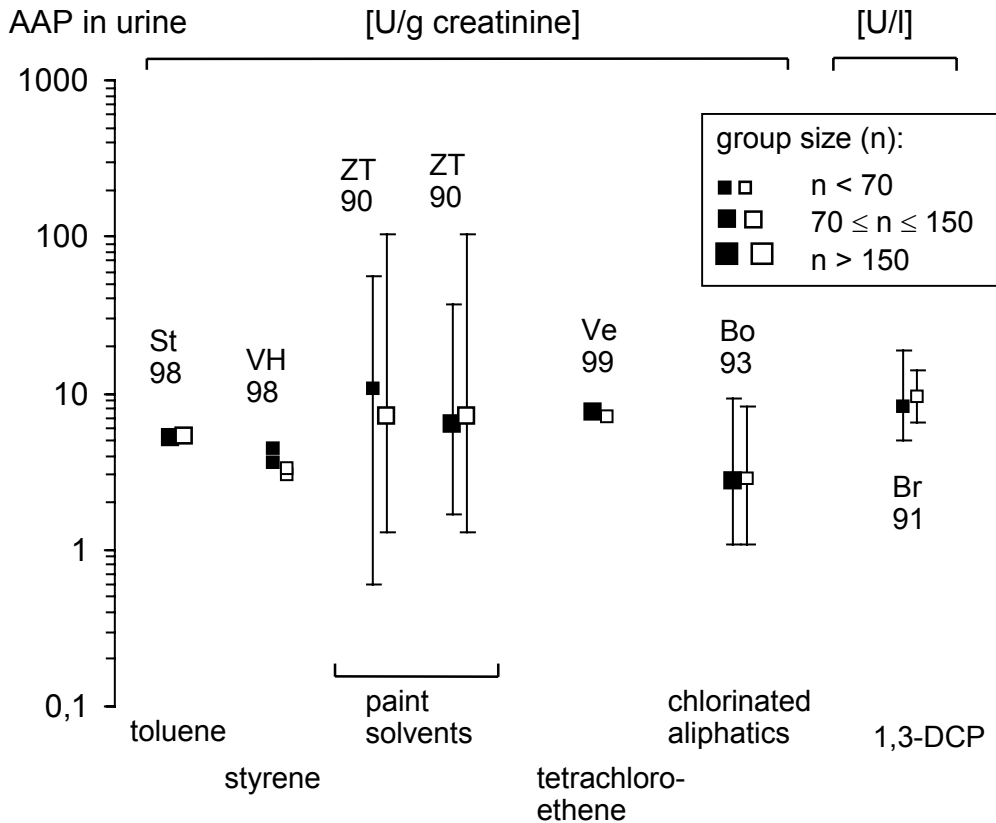


In a study on printers exposed to toluene, STENGEL et al. (1998) observed a statistically significant, but very slight increase in NAG with a cumulative toluene exposure index (ppm years). No interaction between exposure index and hypertension was observed, but the relation for NAG did not persist when hypertensive patients were excluded from the study.

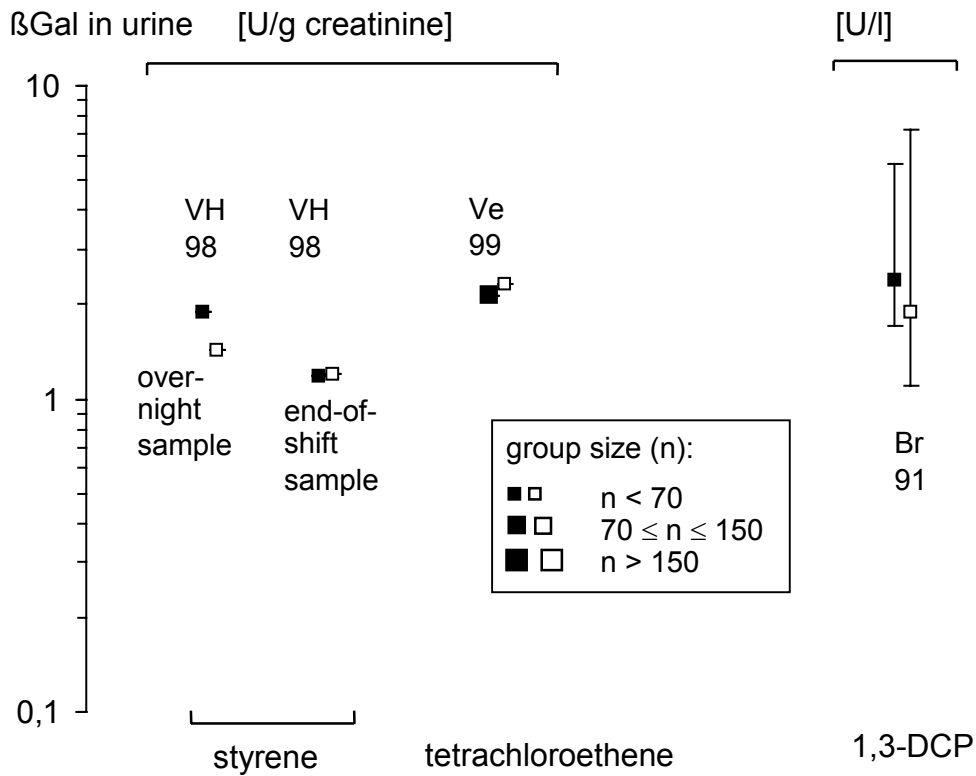
In the studies of VYSKOCIL (1989, 1991), NAG was increased in workers exposed to styrene and petroleum hydrocarbons, respectively. In VYSKOCIL et al. (1991), the increase was found at the end of the last workday of the workweek but not in the arithmetic mean of the four samples per worker which were taken on the first and last day of the workweek upon arrival to work and at the end of the workday. RBP, which is considered to be a more sensitive marker of tubular changes, was not increased. The authors speculate that in this case the increase of NAG may be a result of stimulated exocytosis or increased renal activity rather than a toxic effect. Furthermore, as NAG is a marker of cellular damage, it may reflect rather acute than chronic effects, which is supported by the observed increase only at the end of the workweek in VYSKOCIL et al. (1989).

### 6.3.2.8 Alanine aminopeptidase, $\beta$ -galactosidase, and $\beta$ -glucuronidase

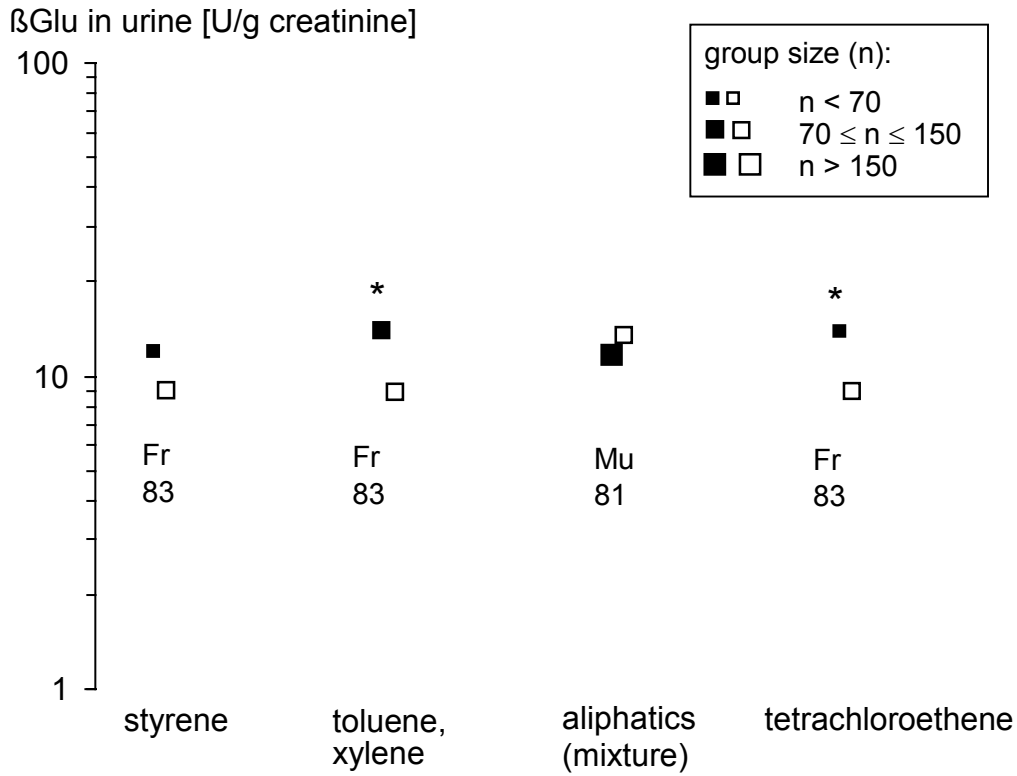
The values of alanine aminopeptidase (AAP),  $\beta$ -galactosidase ( $\beta$ Gal), and  $\beta$ -glucuronidase ( $\beta$ Glu) in urine of solvent-exposed and control workers are compiled in Tab. 9.5, Tab. 9.6, and Tab. 9.8, and the results are summarized in Tab. 6.1 and Fig. 6.1 to Fig. 6.3.



**Fig. 6.1** Comparison of alanine aminopeptidase (AAP) activity in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols). The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Abbreviations of study authors: St98: STENGEL et al. (1998); VH98: VERPLANKE and HERBER (1998); ZT90: ZSCHIESCHE and TRIEBIG (1990); Ve99: VERPLANKE et al. (1999); Bo93: Boogard et al. (1993); Br91: BROUWER et al. (1991). Cf. Tab. 9.6.



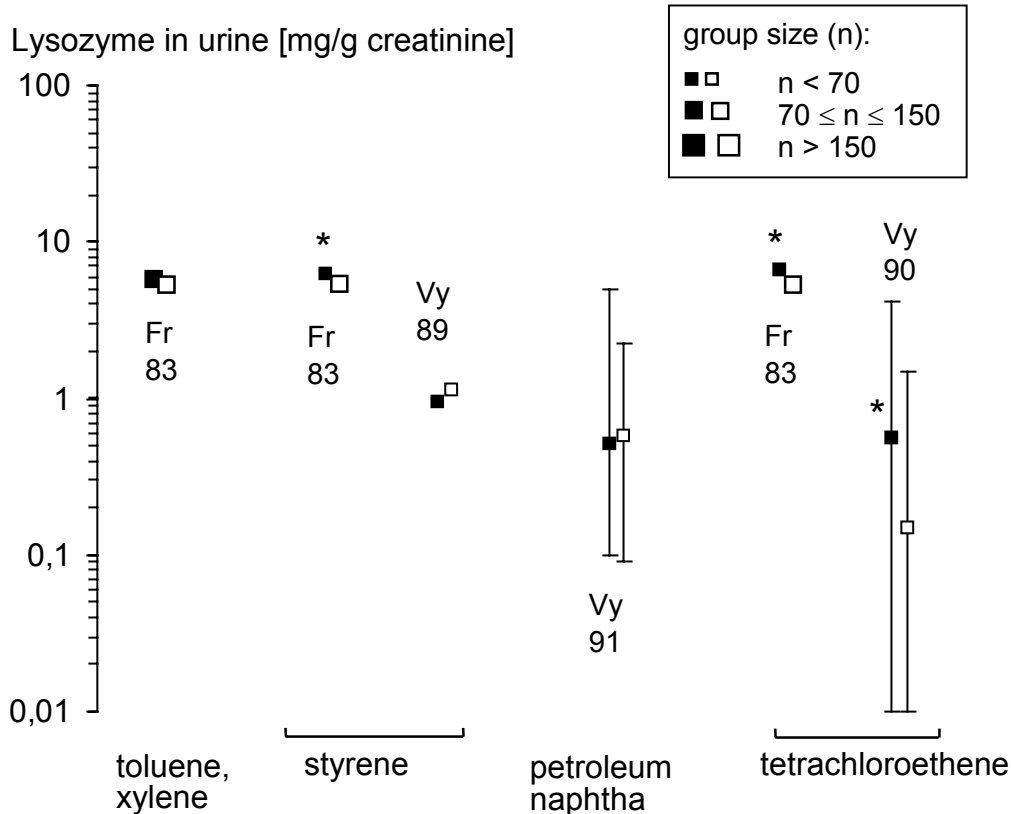
**Fig. 6.2** Comparison of  $\beta$ -galactosidase ( $\beta$ Gal) activity in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols). The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Abbreviations of study authors: VH98: VERPLANKE and HERBER (1998); Ve99: VERPLANKE et al. (1999); Br91: BROUWER et al. (1991). Cf. Tab. 9.5.



**Fig. 6.3** Comparison of  $\beta$ -glucuronidase ( $\beta$ Glu) activity in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols). The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies. Abbreviations of study authors: Fr83: FRANCHINI et al. (1983); Mu81: MUTTI et al. (1981). Cf. Tab. 9.8.

### 6.3.2.9 Lysozyme

The values of lysozyme in urine of solvent-exposed and control workers are compiled in Tab. 9.10, and the results are summarized in Tab. 6.1 and Fig. 6.1.



**Fig. 6.1** Comparison of lysozyme concentration in urine of solvent-exposed workers (full square symbols) and of non-exposed controls (open square symbols). The data points represent mean or median values, bars indicate the range of individual values. Note logarithmical scale. Asterisks indicate statistically significant differences according to the authors of the studies. Abbreviations of study authors: Fr83: FRANCHINI et al. (1983); Vy89: VYSKOCIL et al. (1989); Vy91: VYSKOCIL et al. (1991); Vy90: VYSKOCIL et al. (1990). Cf. Tab. 9.10).

### 6.3.2.10 Tamm-Horsfall protein

Tamm-Horsfall glycoprotein (THG) has only been determined in three studies. In a group of tetrachloroethene exposed workers, an increase in mean urinary THG-excretion was observed (MUTTI et al., 1992). However, a toxic effect on the tubulus is rather expected to decrease the excretion of THG. No explanation for their contrary finding is offered by the authors (MUTTI et al., 1992). Two further studies in paint production workers with mixed solvent exposure (NORMAND et al., 1989, 1990) and in a group of floor layers, printers, and roadmen exposed to several solvents (HOTZ et al., 1990, 1993) found no alterations compared to the corresponding control group (see Tab. 6.1 and Tab. 6.1). Because the solvents in these three studies were rather different, no comparisons between the outcome of these studies can be made.

#### 6.3.2.11 E-selectin in serum

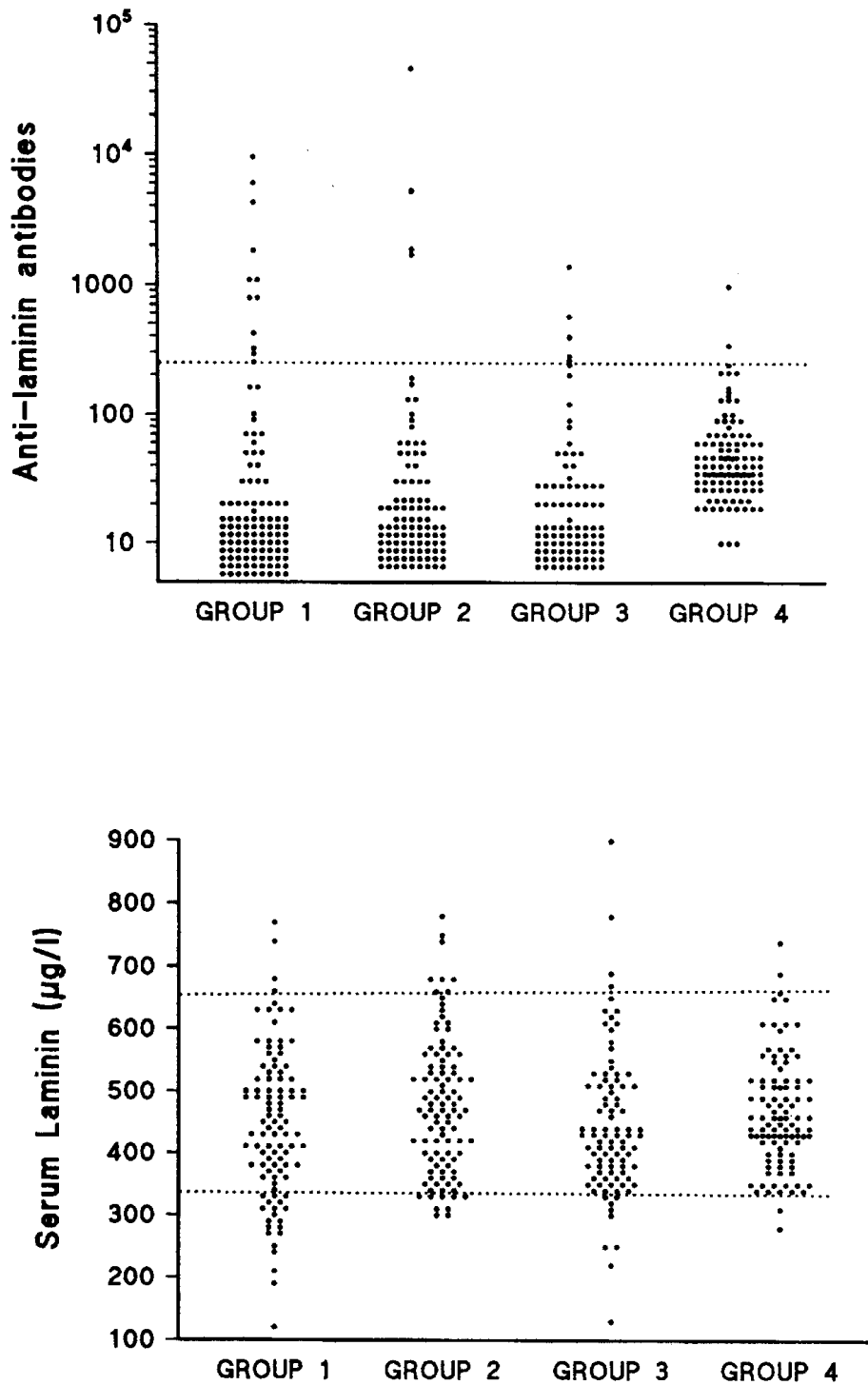
Only one study was identified in which E-selectin in serum, was measured (STEVENSON et al., 1995, see Tab. 6.1). There was a greater proportion of subjects with high levels of soluble E-selectin in two groups of workers from a car manufacturing plant that were exposed to paint solvents or mineral oils, respectively. No increase was found in third group with low exposure to hydrocarbons.

#### 6.3.2.12 Laminin and anti-laminin antibodies

Laminin (as P1-fragments) and/or anti-laminin antibodies (ALAB) in serum have been analysed in several studies (STEVENSON et al., 1995; HOTZ et al., 1993; MUTTI et al., 1992; PRICE et al., 1994, 1995). To illustrate the findings, the dot diagrams from STEVENSON et al. (1995) are shown in Fig. 6.1. In this study, mean laminin levels in serum were not different between several solvent-exposed groups and from controls, but in a subgroup of workers (group 2) exposed to petroleum-based mineral oils a significantly albeit very slightly increased prevalence of raised laminin levels was found. In contrast, in paint-solvent-exposed workers (subgroup 1) there was a tail of low serum laminin levels (STEVENSON et al., 1995).

The group of workers studied by PRICE et al. (1995) is not described in much detail, but it seems that it was in part included in the study of MUTTI et al. (1992). Both studies and PRICE et al. (1994) found an increase of laminin fragments in serum of tetrachloroethene exposed workers. Urinary excretion of laminin fragments were not studied by MUTTI et al. (1992), but such increases were observed in tetrachloroethene and in mixed-hydrocarbon exposed workers by PRICE et al. (1994, 1995).

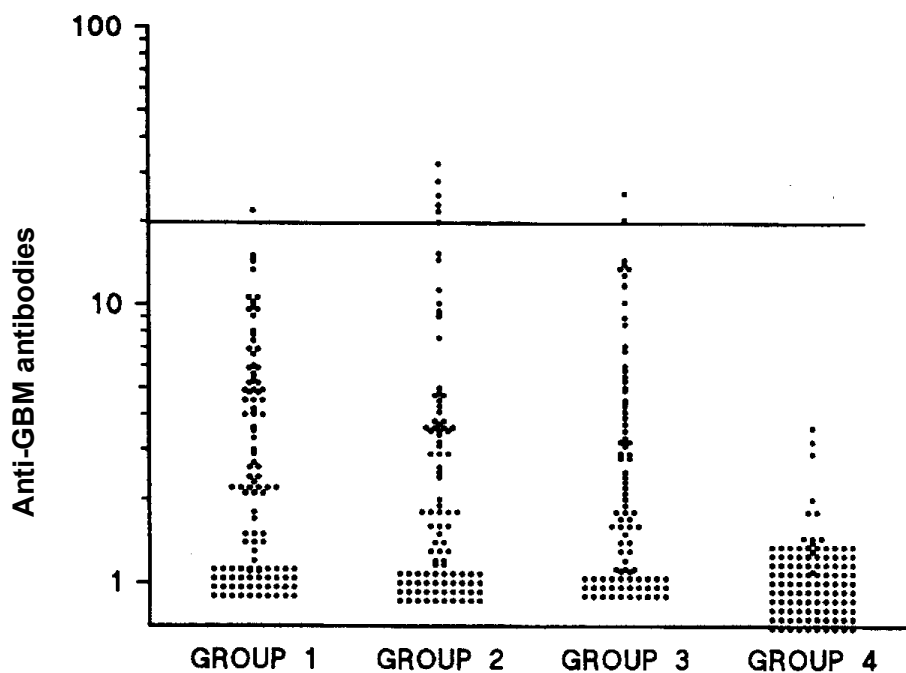
A significantly greater proportion of subjects with high serum levels of ALAB was observed in a subgroup of workers (group 1 in Fig. 6.1) from a car manufacturing plant that were exposed to paint solvents (STEVENSON et al., 1995). Slightly higher titers of ALAB in serum also were found in some individual employees of an oil refinery, in these workers, albumin excretion showed no evidence of renal disease (VIAU et al., 1987). ALAB were also found in some toluene exposed printers, but the incidence was the same in the control group (STENGEL et al., 1998).



**Fig. 6.1** Anti-laminin antibodies (ALAB) (upper part, arbitrary units) and laminin (lower part) in serum in groups of solvent-exposed workers (group 1 - 3) and of non-exposed controls (group 4). Note logarithmic scale for ALAB. Diagrams from STEVENSON et al. (1995). For further details, see text and Tab. 6.1.

### 6.3.2.13 Anti-glomerular basement membrane antibodies

Anti-glomerular basement membrane antibodies (AGBM) have been determined in three studies (MUTTI et al. 1992; STENGEL et al., 1998; STEVENSON et al., 1995). The findings from STEVENSON et al. (1995) are shown as an example in Fig. 6.1. A significant proportion of group 2 (workers exposed to mineral oils) had raised serum AGBM, and in all occupationally solvent-exposed groups (1 - 3) the number of "borderline values" (defined as 10 - 20 units by the manufacturer of the test) were increased. Although, the mean value was increased among tetrachloroethene exposed workers, the frequency of abnormal values was the same among controls (MUTTI et al., 1992). No person positive for AGBM was found in the third study on toluene exposed printers (STENGEL et al., 1998).



**Fig. 6.1** Anti-glomerular basement membrane antibodies (AGBM) in serum (arbitrary units) in groups of solvent-exposed workers (group 1 - 3) and of non-exposed controls (group 4). Note logarithmic scale. Horizontal line indicates a cut-off level quoted by the manufacturer of the clinically validated ELISA-test which was used for determination. Diagrams from STEVENSON et al. (1995). For further details, see text and Tab. 6.1.



### 6.3.3 Evaluation and discussion

HOTZ (1994) has discussed in great length several possible biases that are common in cross-sectional studies such as selection effects, exposure assessment, interactions due to mixtures, turnover and reversibility of the kidney damage. Most of them decrease the study power.

As demonstrated in Tab. 6.1, no parameter was increased consistently after exposure to a certain chemical.

Different exposure concentrations may be one reason for these discrepancies. However, no consistent pattern is emerging. For example, for styrene current exposure concentrations in the different studies as TWA were 86-225 mg/m<sup>3</sup>. Albumin was increased in the studies with a TWA of 113 (47-320) mg/m<sup>3</sup> (VERPLANKE and HERBER, 1998) and with 20-100 mg/m<sup>3</sup> (peaks to 925 mg/m<sup>3</sup>) (ASKERGREN et al., 1981a), which were the studies with the somewhat lower exposure concentrations. Chronic exposure cannot be compared, because years exposed and years employed as measures of chronic exposure are not given in most of the studies. Similarly, for tetrachloroethene at first sight no explanation can be given why, for example, albumin is increased in the study of MUTTI et al. (1992) with a median exposure concentration of 100 mg/m<sup>3</sup>, but not in the study of VYSKOCIL et al. (1990) with exposure to 157 mg/m<sup>3</sup>. Again, chronic exposure cannot be compared due to lack of data.

Also, when comparing differently exposed groups, the authors of the studies in most cases did not find a dose-response-relationship concerning exposure concentration or duration of exposure (ROCSKAY et al., 1993; SOLET and ROBINS, 1991; VERPLANKE et al., 1999; VYSKOCIL et al., 1991). E.g., the prevalence of elevated albuminuria was not related to any specific job title or to the duration of employment (ASKERGREN et al., 1981; 1984, VIAU et al., 1987).

However, as stressed by HOTZ and BOILLAT (1989), a straight dose-response-relationship between exposure and renal damage may be too a simplistic assumption, since peak exposures, intermittent exceeding of thresholds, and latency periods might be as important as intensity and duration of exposure.

Regarding the acute nephrotoxicity of various solvents which has been described in case reports (see 0), the lack of an association of parameters indicating early signs of nephrotoxicity with chronic solvent exposure may be related to short-term higher exposures during chronic exposure which are not reflected by TWA exposure concentrations. In this context, it is worth mentioning that in an experimental study with human volunteers, no changes in urinary albumin and  $\beta_2$ M excretion could be noted after a 6.5 h exposure to 382 mg/m<sup>3</sup> toluene (the Danish TWA-TLV at that time) (KRAEMMER NIELSEN et al., 1985).

Moreover, short-term dermal exposure may be substantial at many solvent-exposed workplaces and may contribute considerably to overall exposure depending on the type of work and the solvent used. Although some studies mention the importance of this route (HASHIMOTO et al., 1991; HAUFROID et al., 1997), dermal exposure was not taken into account or quantified in any cross-sectional study.

Workers with a story of kidney disease or risk factors for developing kidney disease were excluded in several studies. Such selection criteria may be too stringent and lead to an underestimation of an effect. For example, it cannot be ruled out that preexisting increased protein excretion or kidney disease may have been caused by exposure to the chemicals at the workplace. Also, hypertension may either have been caused by exposure to the chemicals or be a risk factor in addition to exposure to solvents. As shown by HOTZ et al. (1990; 1993), workers with hypertension exposed to various solvents are at higher risk for developing abnormal values in various urine parameters than workers without hypertension.

On the other hand, also an overestimation of the effect may occur. Boogard and CAUBO (1994) have shown that increased albumin excretion in a group of workers exposed to chlorinated hydrocarbons may at least partly be related to alterations in the circadian rhythm due to shift-work. Comparing workers with similar shift-work conditions abolished differences in albumin excretion between exposed and control-group workers that had been found in a previous study in which non-shift workers had served as controls (BOOGAARD et al., 1993).

#### 6.3.3.1 Statistical analysis

We investigated the question of statistical significance of a possible difference in urinary excretion of biomarkers in solvent-exposed workers and non-exposed controls using two different approaches. In a first analysis we looked for those studies in which mean (arithmetic or geometric), standard deviation (or standard error of the mean), and sample size are given, so that Student's t-test could be applied to the data. Using the one-tailed test, we found statistical significance exactly for the studies for which significance is also given by the authors, but for no additional study (data not shown). Our second analysis is based on the observation (see Fig. 6.1 to Fig. 6.1 and Tab. 9.1 to Tab. 9.10) that the differences between mean or median values may appear relatively small but maximum values of individuals are partially considerably higher, up to more than two orders of magnitude, in exposed workers than in the corresponding group of non-exposed controls – particularly with regard to the albumin excretion.

**Tab. 6.1** Explorative statistical analysis of the frequency of "high" values for variables of urinary excretion in cross-sectional studies with solvent exposure. "High" means individual values greater than some cut-off limit, where the cut-off limit has been chosen under consideration of the normal ranges given by BOEGE (1998).

| Variable         | Cut-off limit   | Frequency of groups containing individuals with "high" values <sup>1</sup> |             | p-value <sup>2</sup><br>(Fisher's exact test, one-tailed) |
|------------------|---|--|-------------|---|
|                  |   | Exposed  | Non-exposed |   |
| Albumin          | 37 mg/g creatinine <sup>3</sup> , or 19 mg/l urine <sup>3</sup> , resp.   | 14/14 (100 %) <sup>5</sup>   | 7/12 (58 %) | <b>0.01</b>   |
|                  | 100 mg/g creatinine, or 100 mg/l urine, resp.                             | 9/14 (64 %)  | 2/12 (17 %) | <b>0.02</b>   |
| β <sub>2</sub> M | 200 µg/g creatinine <sup>3</sup> , or 300 µg/l urine <sup>3</sup> , resp. | 7/9 (78 %)   | 5/8 (63 %)  | 0.4   |
| NAG <sup>4</sup> | 5 U/g creatinine <sup>3</sup>   | 7/9 (78 %)   | 4/7 (57 %)  | 0.4   |
|                  | 20 U/g creatinine   | 3/9 (33 %)   | 0/7 (0 %)   | 0.2   |

1: Number of studies (groups within a study) in which the upper limit of the range of individual values is greater than the cut-off limit, related to the number of studies for which the range of individual values is given in the paper (data from Tab. 9.1, Tab. 9.2, and Tab. 9.4).

2: Comparison exposed versus non-exposed

3: Upper limit of the normal range of BOEGE (1998)

4: The studies of BROGREN et al. (1986) and RASMUSSEN et al. (1993) were not included in this analysis, because these authors used a different method for the determination of NAG activity.

5: Additional data for these groups can be found in Tab. 6.2.

Therefore, we tried to examine the frequency of "high" individual albumin values in a kind of a meta-analysis. "High" was defined under consideration of the "normal" ranges given by BOEGE (1998) Tab. 4.1. It would have been favorable for such an analysis to have the original data with individual values and the number of urine samples of exposed and non-exposed persons, respectively. Of course, these data usually are not given in the publications. Instead, we used a simplified procedure by counting – over all studies – the number of groups (exposed or non-exposed) in which "high" individual values occur and by relating them to the total number of groups in the studies. The results of the test are given in Tab. 6.1; the p-values for albumin excretion indicate "significance" at the 5%-level. Because of the simplified analysis, which does not allow consideration of the sample sizes of the groups, and because the type of analysis was chosen after inspection of the data, the analysis has a preliminary and "explorative" character only. However, despite these limitations, the comparison of the frequencies of "high" values according to Tab. 6.1 – together with the reported statistical significances in some studies – can be seen as support of the hypothesis (which is mainly based on data from case-control studies, see chapter 6.2) that there may be an association between occupational exposure to organic solvents and renal damage. The effects seem to be shown particularly by

increased urinary albumin excretion and may especially or solely occur after heavy exposures and/or in sensitive subpopulations.

**Tab. 6.2** Solvent-exposed groups with individual values of albumin concentration in urine exceeding normal range (37 mg/g creatinine or 19 mg/l, respectively, according to BOEGE, 1998). Numerical values of albumin excretion are shown in Tab. 9.1.

| Industry/work  | Main compounds  | Reference                 |
|--|---|---------------------------|
| Oil refinery/laboratory technicians, truck drivers, bulk pant and refinery operators | Aliphatic and aromatic hydrocarbons   | VIAU et al. (1987)        |
| Shoe production/gluers   | Petroleum naphtha, toluene  | VYSKOCIL et al. (1991)    |
| Paint manufacturing and spraying   | Toluene   | NG et al. (1990)          |
| Photogravure printing  | Toluene   | ASKERGREN et al. (1981a)  |
| Floor layers   | Toluene and methanol  | HOTZ et al. (1990)        |
| Paint manufacturing  | Xylene/toluene  | ASKERGREN et al. (1981a)  |
| Reinforced plastic industry  | Styrene   | VYSKOCIL et al. (1989)    |
| Plastic boat manufacturing   | Styrene   | ASKERGREN et al. (1981a)  |
| Dry cleaning   | Tetrachloroethene   | VERPLANKE et al. (1999)   |
| Dry cleaning plants  | Tetrachloroethene   | SOLET and ROBINS (1991)   |
| Dry cleaning   | Tetrachloroethene   | VYSKOCIL et al. (1990)    |
| Organochlorine plant/shift workers   | Allyl chloride, epichlorhydrin, 1,3-dichloroprropene, hexachlorocyclopentadiene | BOOGAARD et al. (1993)    |
|  |   | BOOGAARD and CAUBO (1994) |
| Soil fumigation in flower bulb culture   | 1,3-Dichloropropene   | BROUWER et al. (1991)     |

### 6.3.3.2 Analysis of site of action

The question if effects on the kidney occur at the tubular or at the glomerular site was analysed in several studies. Case reports, described in chapter 5, indicate renal damage of tubular origin. However, in cases of acute intoxication exposure generally is high or even excessive. On the other hand, case-control studies (chapter 6.2), where different types of glomerulonephritis have been found to be associated with solvent exposure, point to glomerular damage. In the cross-sectional studies, indications for both locations have been found. It may be possible that, as in other renal diseases, in the early stages mainly the tubuli are affected and damage later progresses to severe interstitial changes with glomerular involvement.

As the outcome of the cross-sectional studies in solvent-exposed workers does not reveal obvious differences with respect to the type of chemicals, some principal findings are demonstrated from the study of MUTTI et al. (1992), which is the most extensive investigation.

In the study of MUTTI et al. (1992), which was carried out on tetrachloroethene-exposed workers, the biochemical and immunochemical abnormalities suggested diffuse structural and functional changes within the kidney, possibly resulting from generalized membrane disturbances caused by the solvent itself or by reactive metabolites (see 3.1.2). At the glomerular level, such an effect would give rise to the release of LAM, FNU and GAGs, possibly resulting in higher glomerular permeability to plasma proteins. From the relative increase in albumin and transferrin compared with IgG, there seems to be a loss of charge rather than of size-selectivity of the glomerular barrier.

Glomerular changes were also reported in groups exposed mainly to

- not further specified solvents during work in refineries (GRUENER et al., 1992);
- mixed paint solvents (NORMAND et al., 1990; YAQOOB et al., 1993);
- aliphatic/aromatic hydrocarbons (HASHIMOTO et al., 1991; VIAU et al., 1987a; YAQOOB et al., 1993);
- toluene or toluene/ xylene mixtures (ASKERGREN et al., 1981a);
- trichloroethene (NAGAYA et al., 1989);
- several organochlorine compounds (BOOGAARD et al., 1993).

Increased shedding of epithelial membrane components from tubular cells with a different location along the nephron is another obvious finding among tetrachloroethene-exposed workers in the study of MUTTI et al. (1992). Interestingly, similar observations of tubular damage with increased excretion of NAG,  $\beta_2$ M and  $\alpha_1$ M were described in a recent case report after heavy oral exposure (BRÜNING et al., 1998). In addition to brush-border antigens derived from the proximal tubules, excretion of other cellular components with different locations along the nephron was significantly increased, namely Tamm-Horsfall protein (THG) from the ascending tract of Henle's loop, GAGs, particularly concentrated at the medullary level, but also present in the extracellular matrix and basement membranes, and TNAP which is diffusely distributed along the nephron.

In other studies, changes in tubular parameters were observed in workers mainly exposed to

- various, not further specified solvents (HOTZ et al., 1989; MEYER et al., 1984);
- mixed paint solvents (NORMAND et al., 1990; YAQOOB et al., 1993; ZSCHIESCHE and TRIEBIG, 1990);
- naphtha blends (ROCSKAY et al., 1993; VYSKOCIL et al., 1991);
- toluene (NG et al., 1990; STENGEL et al., 1998); toluene/xylene (FRANCHINI et al., 1983);

- styrene (VERPLANKE and HERBER, 1998; styrene (VYSKOCIL et al., 1989);
- tetrachloroethene (VERPLANKE et al., 1999);
- trichloroethene (BROGREN et al., 1986; RASMUSSEN et al., 1993);
- 1,3-dichloropropene (BROUWER et al., 1991; OSTERLOH et al., 1993).

#### **6.3.4 Conclusion**

In contrast to the exposed groups, only in very few cases in control groups signs of kidney changes were seen. Therefore HOTZ (1994) has concluded that the results of the cross-sectional studies are compatible with the hypothesis of a nephrotoxic effect of organic solvents at long-term exposure. This conclusion is supported by some further cross-sectional studies that have been published since this review (STEVENSON et al., 1995, VERPLANKE and HERBER, 1998; VERPLANKE et al., 1999) and by the analysis in this report.

A preliminary statistical evaluation made in this report suggests that a high albumin excretion (micro- or macroalbuminuria) more frequently occurs in solvent-exposed groups of workers than in the corresponding control groups. This has been observed in various groups which were exposed to different solvents (toluene, styrene, petroleum hydrocarbons, tetrachloroethene, other haloalkenes) at different workplaces. However, possible effects cannot be ascribed to defined solvents or solvent mixtures.

**Tab. 6.1** Nephrotoxicity of hydrocarbon solvents – cross-sectional studies  
(Studies are arranged in groups according to solvent categories)

| Industry/ work   | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age        | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>   | Remarks | Reference             |
|--|--|--|---|--|---------|-----------------------|
| <b>Mixed solvents</b>  |  |  |   |  |         |                       |
| Refinery   | 117 m<br>37 a<br>not reported<br>not reported                            | 65 m<br>44 a<br>(electrical company workers) | No data on solvents or concentrations reported  | Production workers (n=76):<br><u>Urine</u> : ↑ TRF (> 10 a work only), SOD<br>↔ ALB, NAG<br>maintenance staff (n=42):<br>↔ ALB, NAG, TRF, SOD                |         | GRUENER et al. (1992) |
| Various (e.g. printing, floor layering, dry cleaning, painting, tank cleaning) | 148<br>not reported<br>not reported<br>not reported                      | Controls recruited from whole group studied  | Different solvents (no details given), interquartil groups based on intensity- and duration-graded solvent exposure score (arbitrary units):<br>Q1 (control) 0.0<br>Q2 (low exposure) 1.8<br>Q3 (medium exposure) 11.5<br>Q4 (high exposure) 30.4 | <u>Urine</u> : ↑ NAG, <b>erythrocytes</b> and possibly ALB related to exposure score<br>↔ TP (Shaw's index), leucocyturia<br><br><u>Serum</u> : ↔ creatinine |         | HOTZ et al. (1989)    |

| Industry/ work                              | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed                            | Control<br>No. and sex<br>Average age  | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>   | Remarks  | Reference                      |
|---|---|--|--|--|--|--------------------------------|
| Floor layers<br><br>Printers<br><br>Roadmen | 106<br>35.6 (16 – 62) a<br><br>34<br>44.7 (20 – 63) a<br><br>52<br>51.0 (27 – 62) a<br>not reported | 69<br>31.0 (15 – 54) a<br>(no occupational<br>solvent exposure,<br>no details<br>reported) | Intensity- and duration-graded<br>lifetime exposure score (arbitrary<br>units):<br><u>Floor layers</u> (heavy exposure<br>group, mainly toluene, methanol)<br>21.1<br><br><u>Printers</u> (moderate exposure<br>group, mainly toluene) 18.6<br><br><u>Roadmen</u> (low exposure group,<br>various hydrocarbon mixtures) 12.3 | <u>Urine</u> : ↑ <b>ALB, NAG</b> , RBP<br>related to interaction of<br>exposure and hyper-<br>tension<br>? β <sub>2</sub> M, erythrocytes, ↔<br>THP<br><u>Serum</u> : ↑ <b>LAM</b> related to<br>interaction of exposure<br>and hypertension<br>↓ <u>Creatinine clearance</u><br>related to interaction of<br>exposure and age | Results suggest that<br>"interaction between<br>hypertension and<br>hydrocarbon expo-<br>sure has an influ-<br>ence on kidney<br>function" | HOTZ et al.<br>(1990,<br>1993) |
| Garage/ vehicle<br>mechanics                | 119 m<br>30 (20 – 49) a<br>9.4 (1 – 13.1) a<br>not reported   | 50 m<br>37 (24 – 50) a<br>(non-exposed<br>workers)   | Hydrocarbon mixtures (e.g., petrol<br>fuels, no details reported),<br>intensity- and duration-graded<br>lifetime exposure score (arbitrary<br>units): 4.7  | <u>Urine</u> : ↔ ALB, NAG, RBP   | Compared to HOTZ<br>et al. (1990, 1993),<br>exposure was low   | HOTZ et al.<br>(1997)          |
| Chemical<br>company                         | 25 (no further details<br>reported)   | 68 (hospital or<br>office workers, no<br>details reported)                                 | Multiple solvent exposure (toluene,<br>methyl ethyl ketone,<br>epichlorohydrine, glycidyl ethers,<br>dichloroethane, other)<br>no concentrations reported  | <u>Urine</u> : ↑ <b>mean and<br/>prevalence of elevated<br/>values for NAG</b>   | Similar results for<br>leather finishing wor-<br>kers, no effect in low-<br>exposed laboratory<br>workers                                  | MEYER et<br>al. (1984)         |



| Industry/ work                             | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age                               | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>   | Remarks   | Reference  |
|--|--|---|---|--|---|--|
| Paint production                           | 227 m<br>33.8 ± 9.4 a<br>not reported<br>10.5 ± 7.7 a                    | 193 m<br>30 ± 7.7 a   | Mixed (isophorone, trichloroethene, toluene, xylene, MEK, methanol, isobutanol, white spirit)<br>(no concentrations reported)   | <u>Urine</u> : ↑ <b>ALB, RBP, high values of NAG</b><br>↔ mean NAG, THP, GFR<br><u>Serum</u> : ↓ <b>creatinine</b>   | Only slight alterations; workers had increased lead and cadmium excretion   | NORMAND et al. (1989, 1990)                      |
| Not reported                               | 15 (sex and age not reported)  | 40 m + f,<br>20 – 60 a  | Mixed hydrocarbons (no details reported)  | <u>Serum</u> : ↑ <b>LAM</b>  |   | PRICE et al. (1994)                              |
| Car manufacturing plant/<br>paint sprayers | 112 m<br>45 a<br>21 (13 – 25) a<br>21 (13 – 25) a                        | 92 m<br>42 a<br>(press operators, minimal lubrication oil exposure) | Paint solvents (mainly acetone, MEK, butanol, toluene, xylene, C <sub>9/10</sub> aromatics, various glycols and esters, no concentrations reported)<br>cumulative graded exposure score (arbitrary units): 78 000 | <u>Urine</u> : <b>prevalence of elevated values</b><br>↑ for <b>TP, NAG, γGT, LAP</b><br>↔ for ALB, TRF, RBP<br><br><u>Serum</u> : <b>prevalence of elevated values</b><br>↑ for <b>creatinine</b> | Vapor concentrations below occupational exposure limits; upper reference values of parameters derived from 105 external laboratory based controls without heavy metal or solvent exposure | YAQOOB et al. (1993);<br>PAI et al. (1996, 1998) |

| Industry/ work  | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age  | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>  | Remarks | Reference   |
|---|--|--|---|---|---------|---|
| Car manu-<br>facturing plant/<br>transmission<br>shop | 101 m<br>47 a<br>22 (14 – 27) a<br>22 (14 – 27) a                        | 92 m<br>42 a<br>(press operators,<br>minimal<br>lubrication oil<br>exposure) | Petroleum-based mineral oils<br>(various fractions, no details or<br>concentrations reported)<br>cumulative graded exposure score<br>(arbitrary units): ca. 55 000  | <u>Urine</u> : <b>prevalence of<br/>elevated values</b><br><b>↑ for TP, NAG, LAP,<br/>TRF, RBP</b><br>↔ for ALB, γGT<br><br><u>Serum</u> : prevalence of<br>elevated values<br>↔ for creatinine     |         | YAQOOB et<br>al. (1993);<br>PAI et al.<br>(1996,<br>1998) |
| Car manu-<br>facturing plant/<br>paint sprayers       | 47 m<br>43 a<br>17 (5 – 32) a<br>17 (5 – 32) a                           | 92 m<br>42 a<br>(press operators,<br>minimal<br>lubrication oil<br>exposure) | Paint solvents (mainly acetone,<br>MEK, butanol, toluene, xylene,<br>C <sub>9/10</sub> aromatics, various glycols and<br>esters, no concentrations reported)<br>cumulative graded exposure score<br>(arbitrary units): 57 000 | <u>Urine</u> : <b>prevalence of<br/>elevated values</b><br><b>↑ for TP</b><br>↔ for ALB, NAG, TRF,<br>RBP<br><br><u>Serum</u> : <b>prevalence of<br/>elevated values</b><br><b>↑ for creatinine</b> |         |   |

| Industry/ work  | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age             | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>  | Remarks  | Reference                       |
|---|--|---|---|---|--|---------------------------------|
| Car manu-<br>facturing plant/<br>paint sprayers       | 111 m<br>45 a ± 7.7 a<br>21 a<br>21 a                                    | 108 m<br>41.6 ± 6.4 a<br>(no details<br>reported) | Paint solvents (mostly toluene,<br>xylene, n-butanol, no<br>concentrations reported)<br>cumulative graded exposure score<br>(arbitrary units): ca. 79 000 | <u>Serum</u> : prevalence of<br><b>elevated values</b><br>↑ for ALAB, soluble E-<br>selectin, ↑ for AGBM<br><b>prevalence of lowered</b><br><b>values</b> ↑ for laminin | Same population as<br>YAQOOB et al.<br>(1993) no significant<br>association with<br>elevated serum<br>creatinine or NAG<br>from that study,<br>AGBM associated<br>with higher hydro-<br>carbon exposure<br>score | STEVEN-<br>SON et al.<br>(1995) |
| Car manu-<br>facturing plant/<br>transmission<br>shop | 100 m<br>48.9 a ± 7.0 a<br>22 a<br>22 a                                  | 108 m<br>41.6 ± 6.4 a<br>(no details<br>reported) | Petroleum-based mineral oils<br>(various fractions, no details<br>reported)<br>cumulative graded exposure score<br>(arbitrary units): ca. 54 000          | <u>Serum</u> : prevalence of<br><b>elevated values</b><br>↑ for AGBM, soluble E-<br>selectin, laminin, ↑ for<br>ALAB  |  |                                 |
| Car manu-<br>facturing plant/<br>press operators      | 92 m<br>41.9 a ± 7.0 a<br>19 a<br>22 a                                   | 108 m<br>41.6 ± 6.4 a<br>(no details<br>reported) | Minimal background exposure to<br>hydrocarbons (no details reported)<br>cumulative graded exposure score<br>(arbitrary units): ca. 11 000                 | <u>Serum</u> : prevalence of<br>elevated values<br>↑ for AGBM, ALAB,<br>soluble E-selectin<br>↔ for laminin   | Low exposure; group<br>served as control in<br>YAQOOB et al.<br>(1993)   |                                 |

| Industry/ work                      | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age   | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>            | Remarks   | Reference                      |
|-------------------------------------|--|---|---|---------------------------------|---|--------------------------------|
| Painters                            | 105 m<br>43 (19 – 64) a<br>24 (4 – 44) a<br>not reported                 | 111 m<br>44 (21 – 65) a<br>-<br>27 (15 – 38) a<br>(workmen, no occupational exposure to nephrotoxins) | Mixed (ethyl and butyl acetate, toluene, xylene, ethyl benzene, methyl ethyl ketone, white spirit)<br>ambient air concentration ca. 10 % of MAK, exposure index (TRGS 403) < 1                                | <u>Urine</u> : ↓ TP, NAG, ↔ AAP | Low no. of samples evaluated (n=73 – 79), reasons not reported;<br>no positive correlation with duration or cumulative exposure | ZSCHIE-SCHE and TRIEBIG (1990) |
| Various industry/<br>spray painters | 105 m<br>45 (24 – 65) a<br>26 (8 – 44) a<br>not reported                 |   | Mixed (toluene, xylene, ethyl and trimethyl benzene, C <sub>7</sub> – C <sub>10</sub> aliphatics, acetate esters)<br>ambient air concentration in general < MAK or TLV, exposure index (TRGS 403) < 0.1 – 2.7 | <u>Urine</u> : ↑ TP, NAG, ↔ AAP | No positive correlation with duration or cumulative exposure  |                                |

| Industry/ work  | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age     | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>  | Remarks  | Reference               |
|---|--|---|--|---|--|-------------------------|
| <b>Hydrocarbon mixtures (e.g., white spirits, mineral oils)</b> |  |   |  |   |  |                         |
| Newspaper printing/ pressroom workers                           | 212 m<br>44.6 ± 13.2 a<br>not reported<br>24.9 ± 13.1 a                  | 33 compositors<br>54.2 ± 6.8 a            | Printing and cleaning solutions vapors primarily C <sub>9</sub> -C <sub>14</sub> naphtha aliphatics, small amounts of C <sub>9</sub> -C <sub>10</sub> aromatics, toluene, and xylene; glycol ethers, limonene, pine oil<br><br>Total naphthas in breathing zone: production: 3.4 (0.5 – 67.5) mg/m <sup>3</sup> maintenance and cleaning: 25.2 (7 – 105) mg/m <sup>3</sup> | <u>Urine</u> : ↑ <b>leucocytes, erythrocytes, cellular sediment, ALB</b> (detectable by dipstick), effects ↑ with more frequent use of solvents<br><br><u>Serum</u> : ↔ creatinine, BUN | Association of cellular sediment and Alb↑; high rate of solvent-related dermatitis indicates substantial dermal exposure; all individual findings "clinically within the normal range" | HASHIMOTO et al. (1991) |
| Flexoprint or rotogravure printing                              | 43 m<br>not reported<br>9 – 25 a<br>not reported                         | 43 m<br>not reported                      | Toluene-containing solvent mixtures average exposure 0.5 x TLV (no concentrations reported)  | <u>Urine</u> : ↔ ALB, β <sub>2</sub> M<br><br>↔ creatinine clearance  | Alcohol intake the day before investigation positively correlated with renal excretion rate of Alb   | KRUSELL et al. (1985)   |
| Rubber tire factory   | 32 m<br>29.9 a<br>6.8 a<br>not reported                                  | Sex and age-matched (no details reported) | n-hexane:<br>TWA 43 (9.4 – 137) mg/m <sup>3</sup>  | <u>Urine</u> : ↔ ALB, RBP, β <sub>2</sub> M   | Only summary of results published  | LAUWERYS et al. (1985)  |

| Industry/ work         | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed  | Control<br>No. and sex<br>Average age     | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>  | Remarks   | Reference               |
|------------------------|---|---|---|---|---|-------------------------|
| Metallurgical industry | 33 m<br>42.2 a<br>8.5 a<br>not reported   | Sex and age-matched (no details reported) | White spirit:<br>TWA 91 (8.7 – 388) mg/m <sup>3</sup>   | <u>Urine</u> : ↔ ALB, RBP, β <sub>2</sub> M   | Only summary of results published   | LAUWE-RYS et al. (1985) |
| Car painting factory   | 43 m<br>36 a<br>6 a<br>not reported   | sex and age-matched (no details reported) | White spirit:<br>TWA 42.3 (17 – 83) mg/m <sup>3</sup><br>toluene:<br>TWA 8 (2.3 – 173) mg/m <sup>3</sup>  | <u>Urine</u> : ↔ ALB, RBP, β <sub>2</sub> M   | Only summary of results published   | LAUWE-RYS et al. (1985) |
| Shoe factory           | presently:<br>59 m, 123 f<br>39.4 ± 1.2 a<br>10.2 ± 0.7 a<br>not reported<br><br>previously:<br>10 m, 20 f<br>41.6 ± 1.9 a<br>8.8 ± 0.9 a | 80 (30 m, 50 f)<br>37.9 ± 1.6 a           | C <sub>5</sub> – C <sub>7</sub> aliphatics + alicyclics (n-hexane, cyclohexane, 2- and 3-methyl pentane); acetone, ethyl acetate, methyl ethyl ketone (MEK)<br>TWA ranges:<br>hexanes ≤ 800 mg/m <sup>3</sup><br>cyclohexane ≤ 500 mg/m <sup>3</sup><br>acetone ≤ 400 mg/m <sup>3</sup><br>ethyl acetate ≤ 550 mg/m <sup>3</sup><br>MEK ≤ 260 mg/m <sup>3</sup> | Presently exposed:<br><u>Urine</u> : ↑ TP, ↔ ALB, lysozyme, βGlu<br><u>Serum</u> : ↔ creatinine<br><br>Previously exposed:<br><u>Urine</u> : ↔ TP, ALB, lysozyme, βGlu<br><u>Serum</u> : ↔ creatinine | For 7 workers TP values exceeded mean + 2 SD of controls, and ↑ <b>lysozyme and βGlu</b> were found | MUTTI et al. (1981)     |

| Industry/ work  | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed   | Control<br>No. and sex<br>Average age  | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>   | Remarks  | Reference                 |
|---|--|--|--|--|--|---------------------------|
| Automotive plant/<br>fuel injector<br>calibrators   | I: 157 m, 91 f<br>n.reported<br>2.8 (0.8 – 6.3) a<br>not reported<br><br>II: 119 m, 38 f (from<br>I, reexamined after<br>1 a)<br>37.1 a<br>3.9 (1.8 – 7.3) a<br>not reported | No control group<br>(normal values<br>taken from unex-<br>posed factory<br>workers from pre-<br>vious studies, no<br>details reported) | Naphtha blends; mean<br>concentration at exposure zone:<br>I: 177 mg/m <sup>3</sup> inside<br>40 mg/m <sup>3</sup> outside calibration<br>rooms<br>total range 9 – 590 mg/m <sup>3</sup> ;<br>cumulative exposure 216<br>years mg/m <sup>3</sup><br><br>II: 127 mg/m <sup>3</sup> inside,<br>31 mg/m <sup>3</sup> outside calibration<br>rooms,<br>total range 4 – 790 mg/m <sup>3</sup> ;<br>cumulative exposure<br>269 years mg/m <sup>3</sup> | I: <u>Urine</u> : ↔ total protein,<br>NAG<br>↑ frequency of elevated<br>values for ALB<br><br>II: <u>Urine</u> : ↔ total protein,<br>ALB, NAG, β <sub>2</sub> M,<br><br>Longitudinal analysis<br>between I and II: change<br>in <b>NAG</b> positively associ-<br>ated with recent exposure<br>change; no consistent<br>dose-response | No significant or<br>consistent role of<br>dermal absorption<br>detectable<br><br>„No strong evidence<br>of naphtha-associa-<br>ted renal effects“ | ROCKSKAY<br>et al. (1993) |
| Oil refinery/<br>laboratory<br>technicians, truck<br>drivers, bulk plant<br>and refinery<br>operators | 53 m<br>not reported<br>not reported<br>11 a   | 61 m<br>age-matched  | Various aliphatic (incl. C <sub>4</sub> – C <sub>6</sub> ) and<br>aromatic hydrocarbons<br>total hydrocarbons 8 h TWA at<br>various work sites: mean 4 –<br>72 mg/m <sup>3</sup><br>controls: 0.2 – 2.1 mg/m <sup>3</sup>  | <u>Urine</u> : ↑ <b>ALB</b> , <b>renal<br/>BB50-antigen</b><br>↔ β <sub>2</sub> M, RBP, NAG<br><br><u>Serum</u> : ↑ <b>anti-laminin-AB</b><br>↔ β <sub>2</sub> M; circulating<br>immune complexes  |  | VIAU et al.<br>(1987)     |

| Industry/ work                     | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age   | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>  | Remarks  | Reference                           |
|------------------------------------|--|---|--|---|--|-------------------------------------|
| Shoe production/<br>gluers         | 48 f<br>38 ± 11 a<br>not reported<br>13 (1 – 29) a                       | 23 f<br>34 ± 11 a<br>textile factory<br>workers without<br>history of expo-<br>sure to nephro-<br>toxic chemicals | Mainly petroleum naphtha (3 %<br>aromatics):<br>TWA 1619 (243 – 3737) mg/m <sup>3</sup><br>94 % exposed to > 500 mg/m <sup>3</sup> ;<br>toluene 81 mg/m <sup>3</sup><br>ethyl acetate 160 mg/m <sup>3</sup><br>(11 workers only) | Urine: ↑ <b>NAG (mean and<br/>prevalence of elevated<br/>values)</b> ,<br>↑? TP, LDH, ALB, β <sub>2</sub> M<br>↔ TRF, RBP |  | VYSKOCIL<br>et al. (1991)           |
| <b>Toluene/xylene</b>              |  |   |  |   |  |                                     |
| Photogravure<br>printing           | 42 m<br>42.6 (23 – 62) a<br>not reported<br>not reported                 | 48 workers<br>47.6 (20 – 64) a  | Toluene<br>300 – 400 mg/m <sup>3</sup> (no details<br>reported)  | Urine: ↑? ALB, ↔ β <sub>2</sub> M, ↔<br>osmolality after 14 h fluid<br>deprivation  |  | ASKER-<br>GREN et al.<br>(1981a, b) |
| Paint manu-<br>facturing           | 40 , m<br>52.0 (20 – 64) a<br>not reported<br>not reported               | 48 workers<br>47.6 (20 – 64) a  | Predominantly xylene, toluene<br>TWA 10 – 50 % of Swedish<br>hygiene limits for xylene (350<br>mg/m <sup>3</sup> ) and toluene (300 mg/m <sup>3</sup> )  | Urine: ↑? ALB, ↔ β <sub>2</sub> M,<br>↔ osmolality after 14 h<br>fluid deprivation  |  | ASKER-<br>GREN et al.<br>(1981a, b) |
| Metal working<br>factory/ painters | 118 mostly m<br>40.2 a<br>9.1 a<br>not reported                          | I: 50 f, 30 m<br>37.9 a<br>II: 16 f, 65 m<br>36.8 a   | Toluene, xylene<br>toluene: TWA ca. 95 mg/m <sup>3</sup>   | Urine: ↑ <b>βGlu</b> ,<br>↔ total protein, ALB,<br>lysozyme   | Low HA- and MHA-<br>excretion (mean<br>concentration as in<br>non-exposed) | FRANCHINI<br>et al. (1983)          |



| Industry/ work   | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age   | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>   | Remarks   | Reference                           |
|--|--|---|--|--|---|-------------------------------------|
| Paint manu-<br>facturing and<br>spraying                       | 30 m, 15 f<br>44.8 (25 – 67) a<br>not reported<br>7.5 (1 – 40) a         | 45 (30 m, 15 f)<br>43.1 (25 – 67) a<br>(administration,<br>maintenance,<br>postal work) | Principally toluene<br>air concentration < 380 mg/m <sup>3</sup><br>(no details reported)  | <u>Urine</u> : ↑ <b>RBP</b> (mean and<br>prevalence of elevated<br>values)<br>↔ ALB  | RBP- correlated with<br>o-cresol-, but not<br>with HA-excretion   | NG et al.<br>(1990)                 |
| Photogravure<br>printing                                       | 92<br>38.7 (11.9) a<br>not reported<br>16.3 (13.1) a                     | 74<br>40.0 (9.8) a<br>–<br>16.9 (12.2) a<br>(internal + ex-<br>ternal control)          | Principally toluene<br>air concentration 141 mg/m <sup>3</sup><br><br>(exposure of internal control<br>group: 27 mg/m <sup>3</sup> ) | <u>Urine</u> : ↑? <b>NAG</b><br>↔ ALB, β <sub>2</sub> M, AAP<br><br><u>Serum</u> : ↑ <b>IgE</b><br>↔ AGBM, ALAB, β <sub>2</sub> M<br>↑ creatinine, ↔ β <sub>2</sub> M<br>clearance | Comparison of ALB,<br>NAG, and AAP in<br>longitudinal analysis<br>2 a later showed no<br>alterations of<br>parameters | STENGEL<br>et al. (1998,<br>1999)   |
| <b>Styrene</b>   |  |   |  |  |   |                                     |
| Plastic boat<br>manufacturing                                  | 52 m<br>37.1 (20 – 60) a<br>not reported<br>not reported                 | 48 workers<br>47.6 (20 – 64) a  | Styrene<br>background exposure 20 – 100<br>mg/m <sup>3</sup><br>(peaks up to 925 mg/m <sup>3</sup> )                                 | <u>Urine</u> : ↑ <b>ALB</b> , ↔ β <sub>2</sub> M, ↔<br>osmolality after 14 h fluid<br>deprivation  |   | ASKER-<br>GREN et al.<br>(1981a, b) |
| Boat manufactu-<br>ring, printing,<br>paint manu-<br>facturing | 101 m<br>42.6 (21 – 64) a<br>not reported<br>not reported                | 39 workers<br>47.7 (20 – 64) a  | Boat manufacturing: styrene<br>printing: toluene<br>paint manufacturing: toluene +<br>xylene   | <u>Urine</u> : ↑ <b>erythro- and<br/>leucocytes</b><br><br><u>GFR</u> : ↔ <sup>51</sup> Cr-EDTA<br>clearance   | Only data for com-<br>bined group of<br>workers presented;<br>GFR: 107 workers,<br>48 controls                        | ASKER-<br>GREN<br>(1981c, d)        |

| Industry/ work                             | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age               | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>  | Remarks                           | Reference                   |
|--|--|---|--|---|-----------------------------------|-----------------------------|
| Reinforced plastic industry/<br>laminators | 51 (mostly m)<br>35.9 a<br>6.4 a<br>not reported                         | I: 50 f, 30 m<br>37.9 a<br>II: 16 f, 65 m<br>36.8 a | Styrene<br>TWA 215 mg/m <sup>3</sup>   | <u>Urine</u> : ↑ <b>TP, lysozyme</b><br>↔ ALB, βGlu   |                                   | FRANCHINI et al. (1983)     |
| Polyester producing factory                | 23 m<br>31.8 a<br>1.6 a<br>not reported                                  | Sex and age-matched (no details reported)           | Styrene<br>TWA 86 (34.4 – 189) mg/m <sup>3</sup>   | <u>Urine</u> : ↔ β <sub>2</sub> M, RBP, mean ALB<br>ALB cumulative frequency distribution shifted towards higher values | Only summary of results published | LAUWERYS et al. (1985)      |
| Boat manufacturing                         | 10 m<br>36.9 ± 12.8 a<br>not reported<br>12.6 ± 11.9 a                   | 15 m<br>36.9 ± 10.0 a<br>(cardboard box production) | Styrene<br>TWA 113 (47 – 320) mg/m <sup>3</sup>  | <u>Urine</u> : ↑ <b>RBP, ALB</b><br>↔ NAG, βGal, AAP  |                                   | VERPLANKE and HERBER (1998) |
| Fiberglass laminating plant                | 65 m<br>30 (20–53) a<br>6 a (1–13)                                       | 59 m<br>37 (19-57)<br>(manual workers)              | Styrene<br>TWA 100 mg/m <sup>3</sup> (20-300)<br>evaluated from urinary excretion of mandelic and phenylglyoxylic acid | <u>Urine</u> : ↔ β <sub>2</sub> M, RBP, ALB   |                                   | VIAU et al., (1987b)        |
| Reinforced plastic industry                | 37 f<br>39 ± 10 a<br>not reported<br>11 ± 8 a                            | 35 f<br>39 ± 11 a<br>(administrators, no exposure)  | Styrene<br>TWA 225 (83 – 366) mg/m <sup>3</sup>  | <u>Urine</u> : ↑ <b>NAG</b> (end of last workday only)<br>↔ ALB, β <sub>2</sub> M, RBP, NAG, TP, lysozyme, LDH          |                                   | VYSKOCIL et al. (1989)      |

| Industry/ work                          | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age                 | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>                                    | Remarks  | Reference              |
|---|--|---|---|---|--|------------------------|
| <b>Methyl ethyl ketone (MEK)</b>        |  |   |   |   |  |                        |
| Steel plate painting                    | 23 m<br>29.2 a<br>4 a<br>not reported                                    | Sex and age-matched (no details reported)             | Methyl ethyl ketone:<br>TWA 102 (9.3 – 647) mg/m <sup>3</sup>   | <u>Urine</u> : ↔ ALB, RBP, β <sub>2</sub> M             | Only summary of results published                            | LAUWERYS et al. (1985) |
| <b>Butoxyethanol</b>                    |  |   |   |   |  |                        |
| Beverage package production/ varnishing | 31 m<br>28.8 (22 – 45) a<br>1 – 6 a<br>not reported                      | 21 m<br>33.6 (23 – 49) a<br>(shop and administration) | Butoxyethanol:<br>TWA 2.92 mg/m <sup>3</sup><br>methyl ethyl ketone (no further data)   | <u>Urine</u> : ↔ RBP<br><br><u>Serum</u> : ↔ creatinine | Low exposure (compared to OEL-TWA of 123 mg/m <sup>3</sup> ) | HAUFROID et al. (1997) |
| <b>Ethylene glycol</b>                  |  |   |   |   |  |                        |
| Aviation workers/ de-icing              | 33   | No control group                                      | Ethylene glycol (EG), breathing zone:<br>vapor < 22 mg/m <sup>3</sup> (154 samples)<br>mist 76 – 190 mg/m <sup>3</sup> (3 samples);<br>few samples: di-EG at ca. 1/10 of EG | <u>Urine</u> : ALB, β <sub>2</sub> M, RBP,<br>NAG ↔     | Observation period:<br>2 months                              | GERIN et al. (1997)    |

| Industry/ work                   | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age                                  | Exposure to solvents <sup>1</sup>                                   | Results <sup>2</sup>  | Remarks   | Reference                     |
|----------------------------------|--|--|---|---|---|-------------------------------|
| <b>Tetrachloroethene</b>         |  |  |   |   |   |                               |
| Railroad repair facility workers | 153 (probably m)<br>45.6 (23 – 62) a<br>11.7 (2 – 24) a<br>not reported  | No control group   | Tetrachloroethene<br>mean concentration at workplace<br>35 ± 51 ppm | <u>Urine</u> : ↔ TP, phenol red test; ↓? urine concentration ability<br><br><u>Serum</u> : ↔ urea, creatinine | ≥ 2 a without exposure before study was done; for 68 % of workers, at least one parameter was altered, but no correlation with exposure found | ESSING et al. (1974)          |
| Dry-cleaning                     | 40 (mostly f)<br>43.0 a<br>13.9 a<br>not reported                        | I: 50 f, 30 m<br>37.9 a<br>II: 16 f, 65 m<br>36.8 a                    | Tetrachloroethene<br>TWA ca. 70 mg/m <sup>3</sup>                   | <u>Urine</u> : ↑ βGlu, lysozyme, ↔ total protein, ALB,  |   | FRANCHINI et al. (1983)       |
| Dry-cleaning                     | 2 m, 24 f<br>32.9 (15 - 53) a<br>6.4 (0.1 – 25) a<br>not reported        | 2 m, 31 f<br>34.5 (20 – 57) a<br>(chocolate factory or health service) | Tetrachloroethene<br>TWA 145 (62 – 262) mg/m <sup>3</sup>           | <u>Urine</u> : ↔ ALB, RBP, β <sub>2</sub> M<br><br><u>Serum</u> : ↔ creatinine, β <sub>2</sub> M              |   | LAUWE-RYS et al. (1983, 1985) |

| Industry/ work | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age        | Exposure to solvents <sup>1</sup>                                     | Results <sup>2</sup>   | Remarks | Reference              |
|----------------|--|--|---|--|---------|------------------------|
| Dry cleaning   | 9 m, 41 f<br>40.9 (17 – 65) a<br>10 a<br>not reported                    | 50 blood donors,<br>age- and sex-<br>matched | Tetrachloroethene<br>median 100 mg/m <sup>3</sup> (breathing<br>zone) | <p><u>Urine</u>: ↑ prevalence of<br/><b>elevated values for ALB,<br/>β<sub>2</sub>M, RBP, TRF, IgG,<br/>THG, GAG, HF5, BBA</b><br/>↑ mean for <b>ALB, TRF,<br/>THG, TNAP, GAG, BB50,<br/>HF5, BBA, FNU, LAM</b><br/>↔ total protein, β<sub>2</sub>M, RBP,<br/>IgG, PGE<sub>2</sub>, TXB<sub>2</sub>, PGF<sub>1α</sub>,<br/>PGF<sub>2α</sub>, IAP, NAG</p> <p><u>Serum</u>: ↑ mean for<br/><b>AGBM, LAM</b><br/>↔ creatinine, β<sub>2</sub>M<br/>↑ prevalence of elevated<br/><b>LAM values</b></p> |         | MUTTI et al.<br>(1992) |
| Not reported   | blood 35,<br>urine 20<br>(sex and age not<br>reported)                   | Blood: 40 m + f,<br>20 – 60 a<br>urine: 25   | Tetrachloroethene   | <p><u>Urine</u>: ↑ <b>LAM</b></p> <p><u>Serum</u>: ↑ <b>LAM</b></p>  |         | PRICE et al.<br>(1994) |
| Not reported   | 37 blood<br>50 urine<br>20 – 60 a  | Sex and age<br>matched controls              | Tetrachloroethene   | <p><u>Urine</u>: ↑ <b>LAM</b></p> <p><u>Serum</u>: ↑ <b>LAM</b></p>  |         | PRICE et al.<br>(1995) |

| Industry/ work             | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age                                   | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>  | Remarks   | Reference               |
|----------------------------|--|---|---|---|---|-------------------------|
| Dry-cleaning plants        | 54 m, 138 f<br>not reported<br>11.6 (0 – 49) a<br>not reported           | No control group  | Tetrachloroethene<br>TWA ca. 100 (0 – 950) mg/m <sup>3</sup>  | <u>Urine</u> : no exposure-effect relationship for ALB, TP, and NAG excretion |   | SOLET and ROBINS (1991) |
| Dry cleaning               | 50 m, 32 f<br>34 ± 10 a<br>not reported<br>3.9 (0.1 – 32) a              | 19 (8 m, 11 f)<br>32 ± 7 a<br>(laundry/ dry-cleaning without exposure ) | Tetrachloroethene<br>TWA 7.9 (1 – 221) mg/m <sup>3</sup>  | <u>Urine</u> : ↑ <b>RBP</b><br>↔ NAG, βGal, AAP, ALB, TP                      | No correlation with exposure level  | VERPLANKE et al. (1999) |
| Dry cleaning               | 16 f<br>42 ± 10 a<br>not reported<br>11 (1 – 25) a                       | 13 f<br>42 ± 10 a<br>(administration workers)                           | Tetrachloroethene<br>TWA 157 (9 – 799) mg/m <sup>3</sup>  | <u>Urine</u> : ↑ <b>lysozyme</b><br>↔ ALB, β <sub>2</sub> M, LDH, TP          | No significant correlation of exposure level and urinary parameters found                           | VYSKOCIL et al. (1990)  |
| <b>Trichloroethene</b>     |  |   |   |   |   |                         |
| Metal industry/ degreasing | 82 (not reported)<br>not reported<br>not reported<br>not reported        | 48<br>not reported<br>(workers from fertilizer plant)                   | Chlorinated solvents:<br>trichloroethene (Tri, main compound), freon 113, trichloroethane<br>no further data reported | <u>Urine</u> : ↑ <b>NAG</b>   | Increased values in subgroup currently and previously exposed to Tri, no correlation to urinary TCA | BROGREN et al. (1986)   |

| Industry/ work                              | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age               | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>  | Remarks  | Reference               |
|---|--|---|---|---|--|-------------------------|
| Metal or semi-conductor factory/ degreasing | 104 m<br>36.6 (17 – 63) a<br>not reported<br>8.4 (1 – 34) a              | 102 m<br>37.5 (18 – 65) a<br>(workers and students) | Trichloroethene<br>mean exposure 80 mg/m <sup>3</sup>   | <u>Urine</u> : ↑ TP<br>↔ β <sub>2</sub> M   | 2 controls/2 workers with dipstick-“obvious proteinuria” excluded from study | NAGAYA et al. (1989)    |
| Metal industry/ degreasing                  | 99 (not reported)<br>39.4 (19 – 68) a<br>< 1 – 35.6 a<br>not reported    | No control group                                    | Chlorinated solvents:<br>trichloroethene (main compound),<br>freon 113<br>biological monitoring: ca. 40 – 60 mg TCA/l urine | <u>Urine</u> : <b>NAG</b> ↑ with increasing duration of exposure (non-significant when age and alcohol considered as confounders) | 4 groups with increasing duration of exposure                                | RASMUSSEN et al. (1993) |
| Metal industry/ degreasing                  | 25 m, 4 f<br>41 (20 – 66) a<br>6.2 a<br>not reported                     | No control group                                    | Trichloroethene<br>TWA mean: 27 mg/m <sup>3</sup>   | <u>Urine</u> : NAG ↔  | Reference values from analytical laboratory used for comparison              | SELDEN et al. (1993)    |
| <b>1,3-dichloropropene</b>                  |  |   |   |   |  |                         |
| Soil fumigation in flower bulb culture      | 14<br>42 a<br>during season, July to October                             | Same workers analysed before season                 | 1,3-dichloropropene   | <u>Urine</u> : ↔ β <sub>2</sub> M, AAP, βGal<br>↑ <b>ALB, RBP</b><br><u>Serum</u> : ↔ creatinin, β <sub>2</sub> M                 | Workers monitored before and after working season                            | BROUWER et al. (1991)   |

| Industry/ work                          | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age                                     | Exposure to solvents <sup>1</sup>   | Results <sup>2</sup>   | Remarks   | Reference                   |
|---|--|---|---|--|---|-----------------------------|
| Soil fumigation in agriculture          | 16 m<br>not reported   | –   | 1,3-dichloropropene (1,3-DCP)<br>concentration in air 0.26 – 9.39 mg/m <sup>3</sup> ;<br>exposure 120 – 697 min/subject;<br>mean 3CNAC-metabolite excretion 2466 µg/d                                 | <u>Urine:</u><br>↔ ALB, RBP, NAG<br>(creatinine corrected)<br>↑ RBP, NAG, ↔ ALB<br>(high vs. low CNAC-excretion) | acute effects on one day, measures at 5 intervals prior to, during, and after application;<br>workers previously exposed to 1,3-DCP | OSTERLOH and FELDMAN (1993) |
| <b>Several organochlorine compounds</b> |  |   |   |  |   |                             |
| Organochlorine plant/shift workers      | 73 m<br>36.4 a<br>not reported<br>8.2 (0.5 – 23) a                       | 35 m<br>42.3 a<br>(material division, day work, no exposure to chemicals) | Several organochlorine compounds<br>TWA:<br>allyl chloride < 3 mg/m <sup>3</sup><br>1,2-dichloropropene < 2 mg/m <sup>3</sup><br>epichlorhydrin < 1 mg/m <sup>3</sup><br>HCP < 0.25 mg/m <sup>3</sup> | <u>Urine:</u> ↑ ALB<br>↔ AAP, NAG, RBP, TP   |   | BOO-GAARD et al. (1993)     |



| Industry/ work                           | Exposed<br>No. and sex<br>Average age<br>Years exposed<br>Years employed | Control<br>No. and sex<br>Average age  | Exposure to solvents <sup>1</sup>  | Results <sup>2</sup>  | Remarks   | Reference                            |
|--|--|--|--|---|---|--------------------------------------|
| Organochlorine<br>plant/shift<br>workers | 93 m<br>38.1 a<br>not reported<br>not reported                           | I: 60 m<br>38.9 a (petroleum<br>refinery, shift-<br>work)<br>II: 50 m<br>39.7 a (mainte-<br>nance division,<br>day work) | Several organochlorine<br>compounds:<br>allyl chloride; 1,2-dichloropropene;<br>epichlorhydrin; hexachloro-<br>cyclopentadiene (HCP) | Comparison to group I:<br><u>Urine</u> : ↔ ALB, AAP, NAG,<br>β <sub>2</sub> M<br><u>Serum</u> : ↔ creatinine<br><br>Comparison to group II:<br><u>Urine</u> : ↑ <b>ALB</b> , ↔ AAP,<br>NAG, β <sub>2</sub> M<br><u>Serum</u> : ↔ creatinine | Exposure concentra-<br>tions not reported,<br>but similar to<br>BOOGAARD et al.<br>(1993);<br>albuminuria possibly<br>related to shift-work,<br>not to organochlorine<br>exposure | BOO-<br>GAARD and<br>CAUBO<br>(1994) |

<sup>1</sup>: values in ppm were transferred to mg/m<sup>3</sup> (molar volume 24.1 l at 20 °C); for white spirit 1 ppm ≡ 5.8 mg/m<sup>3</sup> (assuming an average molecular mass of 140 g/mol).

<sup>2</sup> ↔: no effect, ?: possible effect; ↓: decreased, ↑: increased values compared to control.

**Bold symbols** indicate statistically significant difference compared to data for control group.

## 7 Overall Evaluation

### 7.1 Evidence for an association between solvent exposure and renal effects

In many case reports, acute tubular necrosis following solvent exposure has been described. Since the tubular lesion occurs rapidly – usually within a few days after exposure – the relationship between exposure and effect is easily recognizable.

Besides the well-known nephrotoxic haloalkanes (esp. tetrachloromethane), other solvents that have been reported to cause acute renal failure include ethylene glycol and diethylene glycol, toluene, and, in a few cases, xylene, petroleum distillates including diesel fuel, and tri- and tetrachloroethene. In the majority of these cases, acute intoxication occurred after oral ingestion of large amounts of liquid or after heavy inhalative exposure in solvent abuse ("sniffing") or several hours of excessive occupational exposure without protection in badly ventilated small rooms. Therefore, although these cases demonstrate the nephrotoxic potential of acute high exposure, they may be of little relevance with respect to the nephrotoxicity of a long-term low exposure to solvents under conditions at today's workplaces.

Glomerular damage has also been reported to occur after exposure to a variety of solvents, e.g. toluene or Stoddard solvent, or solvent-containing products such as paints and thinners. Several reports state a relationship between chronic solvent exposure and the outbreak of glomerulonephritis. However, exposure to solvents is widespread while glomerulonephritis is rare, and results from such case reports may be due to mere coincidence. Therefore, case reports can only be seen as a starting point for hypothesis generation for epidemiological studies.

Retrospective cohort mortality studies on workers in various solvent-related industries have been carried out. However, these studies focussed on cancer, and only some studies presented data for non-cancer renal diseases. None of the studies reported an excess risk of death for the broad diagnostic categories "genitourinary diseases" or "nephritis and nephrosis". Instead, in several studies a decreased risk was noted which is likely to be explained by the "healthy worker effect". Generally, an evaluation of these studies is complicated by several difficulties, i.e., low study power, inadequate diagnostic categories, inappropriate endpoint, and rough exposure estimates. In summary, the available cohort mortality studies do not seem adequate to reveal an association between solvent exposure and renal disease.

Most evidence for an association between solvent exposure and renal disease comes from case-control studies. In a number of these studies, an association between glomerulonephritis (GN) and occupational exposure to solvents was observed. Although the individual studies may suffer from bias and confounding, it seems unlikely that the association can be fully explained by these factors.

In a recently published meta-analysis (RAVNSKOV, 2000), the overall evaluation of all studies combined indicated a positive association between solvent exposure and

glomerulonephritis with a significantly albeit weakly increased odds ratio (OR) of about 1.6. Additionally, there is some evidence from several case-control studies and from that meta-analysis that exposure to solvents or hydrocarbons, instead of being associated with the original development of glomerulonephritis, may contribute to the advancement of disease in patients with diagnosed glomerulonephritis. In this case, the calculated ORs from a combined analysis range from 1.0 (i.e., no differences between case and control group) for groups with early or acute glomerulonephritis to a significantly increased OR of about 2.2 for groups with chronic renal failure and also for groups with end-stage renal disease. For the latter group, an even higher OR of 5.9 was found when the considerable drop-out rate due to death in some of the studies was taken into account, but the number of studies is too small to draw firm conclusions in this case.

At present, it seems not possible to definitively identify forms of GN that may be specifically related to solvent exposure. Further, it is not possible to identify individual solvents (or specific high-risk groups within occupationally solvent-exposed workers) which may present a higher risk for GN, as the exposure to solvents has only been characterized in a broad way and there are insufficient data on exposure to individual solvents.

Cross-sectional studies in solvent-exposed workers have revealed a complex result. Renal alterations, indicating effects both at the tubular and the glomerular site, were seen in some studies, while no such alterations were found in others. A comparison of the results from the great number of studies is hampered by the fact that the study groups differed with respect to the working site, the type of solvents used, the concentration, frequency and duration of exposure, and the parameter used to monitor renal alterations. However, in contrast to the exposed groups, only in very few cases in control groups signs of kidney changes were seen. Therefore, in accordance with the conclusion made by HOTZ (1994), the results of the cross-sectional studies are compatible with the hypothesis of a nephrotoxic effect of organic solvents. This conclusion is further supported by some further cross-sectional studies that have been published since HOTZ' review (STEVENSON et al., 1995, VERPLANKE and HERBER, 1998; VERPLANKE et al., 1999).

A statistical evaluation made in this report (see Tab. 6.1) suggests that high individual albumin concentrations in urine (micro- or macroalbuminuria) more frequently occur in solvent-exposed groups of active workers than in control groups. It is known that heavy exercise and possibly other factors such as shift-work may lead to an enhanced albumin excretion in urine, but it seems unlikely that these factors or others related to study-design (e.g., different size of exposed and control group) can explain the observed relationship. The groups in which the effect was observed had been exposed at different workplaces to different solvents or solvent mixtures mainly containing toluene, styrene, petroleum hydrocarbons, naphtha, tetrachloroethene, or other haloalkenes, respectively.

## 7.2 Parameters for biological effect monitoring at solvent-exposed workplaces – general recommendations

Broad batteries of tests have been developed including very sensitive end-points and site-specific biomarkers useful to characteristic toxic damage to the kidney at the tissue, cellular and molecular level. For routine measurements, however, only few markers should be tested.

Albumin is proposed by several authors as suitable glomerular marker for routine analysis in occupational exposure. Preliminary data from this study suggest that a high albumin excretion (micro- or even macroalbuminuria) may be more common in groups of workers at solvent-exposed workplaces. Albumin is widely used as a sensitive predictor of diabetic nephropathy and the predictive value of this test has been documented by a number of clinical studies (LAUWERYS and BERNARD, 1989). Microalbuminuria, i.e. a moderately increased concentration of albumin in urine (see Tab. 4.1), can easily be detected by semiquantitative analysis using special test strips which are commercially available. In contrast to other markers, where the diagnostic significance is still unclear, even moderate albuminuria is viewed as an early marker for disease. However, it must be considered that besides renal disease, high albumin excretion is associated also with an increased risk of cardiovascular disease (BERNARD et al., 1997).

BERNARD and LAUWERYS (1991) recommend as a minimum the combination of the determination of at least two proteins, albumin or transferrin as representatives of the high molecular weight class, and RBP as representative of the low molecular weight class. Similarly, HOTZ (1990) proposed that excretion of albumin, NAG, and RBP in urine, supplemented by creatinine clearance, are the most useful markers in field studies on solvent-exposed workers. According to MUTTI (1999), a core battery of urinary markers, among those commercially available should include albumin, one low molecular weight protein, such as  $\beta_2$ M or RBP, and one marker of cytolysis such as the activity of the lysosomal enzyme NAG. Furthermore, creatinine should be determined as a measure of urine concentration. According to PRICE (2000), in addition, a test for infection should be performed. This corresponds quite closely to the core battery of tests recommended by the US Department of Health, which further includes alanine aminopeptidase as a marker (PRICE et al., 1977).

Our analysis has shown that frequently the prevalence of abnormal values may be increased, even if mean or median values were not statistically different. Therefore, if groups of controls and solvent-exposed workers are to be compared, besides median concentrations and ranges, the prevalence of abnormal values should be analysed, for example, values higher than the mean plus 2 standard deviations of the values found in the control group, or compared to the 95 percentile of control values. Furthermore, a comparison should be made to control values of the general population as given above for some of the parameters. Small deviations from reference values cannot be interpreted at the individual level, since alternative explanations are possible.

If increased prevalences of abnormal renal biomonitoring values are found repeatedly in a group of solvent-exposed workers, efforts should be made to identify the

underlying agents and to reduce the exposure. Follow-up examinations of the subjects identified by these tests are also indicated in order to define the predictive value (LAUWERYS and BERNARD, 1989). If one parameter is found consistently to be prevalent, one can probably conclude that the group is or has been exposed to a renal stress (LAUWERYS and BERNARD, 1989).

Tests that reflect glomerular integrity might theoretically have greater prognostic value than those that allow one to assess the integrity of the tubules, since the latter can easily regenerate, at least after acute injury. Furthermore, the glomerular filter is essential for maintaining the plasma pool of proteins, and extensive injury to that structure may have direct metabolic consequences.

In contrast, proteinuria of tubular origin per se usually has no major pathological consequence, since it simply corresponds to a shift in renal disposal of low molecular weight proteins from intracellular catabolism to urinary elimination, and the resulting loss of amino acids is metabolically insignificant (LAUWERYS and BERNARD, 1989).

### **7.3 Future research needs**

The evaluation of cross-sectional studies suggests that high individual concentrations of albumin in urine (clinically evident as micro- or macroalbuminuria) may be more common in groups of solvent-exposed workers. Since the data presented in these cross-sectional studies only allowed for a preliminary statistical analysis, further studies are necessary to confirm or reject this hypothesis, and the prognostic value of such alterations should be investigated in follow-up studies.

Many types of glomerulonephritides represent a severe, irreversible disease that may progress to terminal renal insufficiency requiring life-long dialysis or kidney transplantation (ESRD). Results from case-control studies give some evidence that the progression of glomerulonephritis could be favored by continued exposure to solvents. Further epidemiological studies should be conducted which are especially addressed to investigate this relationship. A possible way could be to compare the course of disease in two groups of GN-patients with continued and discontinued solvent exposure in a follow-up study.

Recent studies suggest that chronic renal disease including glomerulonephritis could be associated not only with occupational solvent exposure, but also with exposure to silica and other inorganic silicon-containing compounds. Some case-control studies (ROSENMAN et al., 2000; NUYTS et al., 1995; GREGORINI et al., 1993; STEENLAND et al., 1990) have found an association with chronic renal failure in patients with or without silicosis; and in cross-sectional studies (HOTZ et al., 1995; NG et al., 1992; BOUJEMAA et al., 1994), alterations of renal biomarkers were described in workers exposed to silica-containing dusts (see ELSEVIERS and DE BROE, 1998, for a brief summary). Further studies are necessary to assess the role of such exposure in the development of renal diseases.

## 8 References

- Adamson CL, Kumar S, Sutcliffe H, France MW, Boulton AJM** (1993) Screening strategies in the detection of microalbuminuria in insulin-dependent diabetic patients. *Prac Diabetes* 10: 142-144
- Albrecht WN, Boiano JM, Smith RD** (1987) IgA glomerulonephritis in a plumber working with solvent-based pipe cement. *Ind Health* 25: 157-158
- Anders MW, Dekant W** (1998) Gluthatione-dependent bioactivation of haloalkenes. *Ann Rev Pharm Toxicol* 38: 501-537
- Asal NR, Cleveland HL, Kaufman C, Nsa W, Nelson DI, Nelson RY, Lee ET, Kingsley B** (1996) Hydrocarbon exposure and chronic renal disease. *Int Arch Occup Environ Health* 68(4): 229-235
- Askergen A** (1981) Studies on kidney function in subjects exposed to organic solvents. III. Excretion of cells in the urine.. *Acta med Scand* 210: 103-106
- Askergen A** (1981) Studies on kidney function in subjects exposed to organic solvents. IV. Effect on 51-Cr-EDTA clearance. *Acta med Scand* 210: 373-376
- Askergen A, Allgen LG, Bergstroem J** (1981) Studies on kidney function in subjects exposed to organic solvents. II. The effect of desmopressin in a concentration test and the effect of exposure to organic solvents on renal concentrating ability. *Acta med Scand* 209: 485-488
- Askergren A, Allgén LG, Karlsson C, Lundberg I, Nyberg E** (1981) Studies on kidney function in subjects exposed to organic solvents. I. Excretion of albumin and beta-2-microglobulin in the urine. *Acta med Scand* 209: 479-483
- Auzepy P, Taktak H, Toubas PL, Deparis M** (1973) Intoxications aiguës par l'éthylène glycol et le diéthylène glycol chez l'adulte. *Sem Hop Paris* 49: 1371-1374
- Ayres PH, Taylor DW** (1989) Solvents. In: Hayes AW (ed.) *Principles and methods of toxicology*. New York, N.Y., Raven Press 111-135
- Baetcke KP, Hard GC, Rodgers IS, McGaughy RE** (1991) Alpha-2<sub>μ</sub>-Globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. U.S. EPA, Washington, D.C.. EPA/625/3-91/019F
- Bahner U, Heidland A** (1998) Toxische Nephropathien. In: Classen M, Diehl V, Kochsiek K (ed.) *Innere Medizin*. München, Urban, Schwarzenberg
- Baldamus CA, Pollok M** (1998) Glomeruläre Nierenerkrankungen. In: Classen M, Diehl V, Kochsiek K (ed.) *Innere Medizin*. München, Urban, Schwarzenberg
- Barrientos A, Ortuno MT, Morales JM, Martinez Tello F, Rodicio JL** (1977) Acute renal failure after use of diesel fuel as shampoo. *Arch Int Med* 137: 1217-1217

- Beirne GJ** (1972) Goodpasture's syndrome and exposure to solvents. *J Am Med Assoc (JAMAA)* 222: 1555
- Beirne GJ, Brennan JT** (1972) Glomerulonephritis associated with hydrocarbon solvents. Mediated by antiglomerular basement membrane antibody. *Arch Environ Health* 25: 365-369
- Bell GM, Doig D, Thompson D, Anderton JL, Robson JS** (1985) End-stage renal failure associated with occupational exposure to organic solvent. *Proc Eur Dial Trans Assoc* 22: 725-729
- Bell GM, Gordon AC.H, Lee P, Doig A, MacDonald MK, Thomson D, Anderton JL, Robson JS** (1985) Proliferative glomerulonephritis and exposure to organic solvents. *Nephron* 40: 161-165
- Bengtsson U** (1985) Glomerulonephritis and organic solvents. *Lancet* 566
- Bennett RH, Forman HR** (1980) Hyypokalemic periodic paralysis in chronic toluene exposure. *Arch Neurol* 37: 673
- Bernard A, Lauwerys R** (1989) Epidemiological application of early markers of nephrotoxicity. *Toxicol Lett* 46: 293-306
- Bernard A, Lauwerys R** (1991) Proteinuria: changes and mechanisms in toxic nephropathies. *Crit Rev Toxicol* 21: 373-405
- Bernard A, Stolte H, de Broe ME, Mueller PW, Mason H, Lash LH, Fowler BA** (1997) Urinary biomarkers to detect significant effects of environmental and occupational exposure to nephrotoxins. IV. Current information on interpreting the health implications of tests. *Ren Fail* 19(4): 553-566
- Bernauer U, Birner G, Dekant W, Henschler D** (1996) Biotransformation of trichloroethene: dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. *Arch Toxicol* 70(6): 338-346
- Berndt WO** (1981) Use of renal function tests in the evaluation of nephrotoxic effects. In: Hook JB (ed.) *Toxicology of the kidney*. Target organ toxicology series. New York, Raven Press 1-29
- Bernis P, Hamels J, Quoidbach A, Mahieu P, Bouvy P** (1985) Remission of goodpasture's syndrome after withdrawal of an unusual toxic. *Clin Nephrol* 23: 312-317
- Blair A, Stewart PA, Tolbert PE, Grauman D, Moran FX, Vaughn J, Rayner J** (1990) Cancer and other causes of death among a cohort of dry cleaners. *Brit J Ind Med* 47: 162-168

**Blumberg A, Huser B, Kuehni M, Muehlethaler JP, Burger HR** (1987) Diagnose glomerulaerer und nicht-glomerulaerer Erythrozyturien mit Hilfe der Phasenkontrastmikroskopie des Urinsedimentes. *Schweiz Med Wschr* 117: 1321-1325

**Boege F** (1998) 12.6 Urinary proteins. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 362-366

**Boice JD, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK** (1999) Mortality among aircraft manufacturing workers. *Occup Environ Med* 56: 581-597

**Bombassei GJ, Kaplan AA** (1992) The association between hydrocarbon exposure and anti-glomerular basement membrane antibody mediated disease (Goodpasture's syndrome). *Am J Ind Med* 21: 141-153

**Bomhard E, Marsmann M, Rühl-Fehlert C, Zywiets A** (1990) Relationships between structure and induction of hyaline droplet accumulation in the renal cortex of male rats by aliphatic and alicyclic hydrocarbons. *Arch Toxicol* 64: 530-538

**Bonzel KE, Müller-Wiefel DE, Ruder H, Wingen AM, Waldherr R, Weber M** (1987) Antiglomerular basement membrane antibody-mediated glomerulonephritis due to glue sniffing. *Eur J Pediatr* 146: 296-300

**Boogaard PJ, Caubo ME** (1994) Increased albumin excretion in industrial workers due to the shift work rather than to prolonged exposure to low concentrations of chlorinated hydrocarbons. *Occup Environ Med* 51(9): 638-641

**Boogaard PJ, Rocchi PS.J, van Sittert NJ** (1993) Effects of exposure to low concentrations of chlorinated hydrocarbons on the kidney and liver of industrial workers. *Brit J Ind Med* 50: 331-339

**Borghoff SJ, Andersen ME, Conolly RB** (1991) Protein nephropathy and kidney cancer in male rats: qualitative and quantitative issues and human relevance. *Chem Indust Inst Toxicol* 11: 1-8

**Bosch X, Campistol JM, Montoliu J, Revert L** (1988) Myelofibrosis and focal segmental glomerulosclerosis associated with toluene poisoning. *Hum Toxicol* 7: 357-361

**Boujema W, Lauwerys R, Bernard A** (1994) Early indicators of renal dysfunction in silicotic workers. *Scand J Work Environ Health* 20: 188-191

**Brautbar N, Barnett A** (1999) Hydrocarbon exposure and chronic renal disease. *Environ Epi Tox* 1: 163-166

**Brogren CH, Christensen JM, Rasmussen K** (1986) Occupational exposure to chlorinated organic solvents and its effect of the renal excretion of N-acetyl-beta-d - glucosaminidase. *Arch Toxicol Suppl* 9: 460-464



**Brouwer EJ, Evelo CT.A, Verplanke AJ.W, van Welie RT.H, de Wolff FA** (1991) Biological effect monitoring of occupational exposure to 1,3-dichloropropene: effects on liver and renal function and on glutathione conjugation. *Brit J Ind Med* 48: 167-172

**Brown DP, Kaplan SD** (1987) Retrospective cohort mortality study of dry cleaner workers using perchloroethylene. *J Occup Med* 29(6): 535-541

**Brüning T, Vamvakas S, Makropoulos V, Birner G** (1998) Acute intoxication with trichlorethene: clinical symptoms, toxicokinetics, metabolism, and development of biochemical parameters for renal damage. *Toxicol Sci* 41(2): 157-165

**Cagnoli L, Casanova S, Pasquali S, Donini U, Zucchelli P** (1980) Relation between hydrocarbon exposure and the nephrotic syndrome. *Brit Med J* 19: 1068-1069

**Cahen R, Francois B, Trollet P, Gilly J, Parchoux B** (1989) Aetiology of membranous glomerulonephritis: a prospective study of 82 adult patients. *Nephrol Dial Transplant* 4(3): 172-180

**Calvery HO, Klumpp TG** (1939) The toxicity for human beings of diethylene glycol with sulfanilamide. *South Med J* 32(11): 1105-1109

**Carlier B, Schroeder E, Mahieu P** (1980) A rapidly and spontaneously reversible Goodpasture's syndrome after carbon tetrachloride inhalation. *Acta Clin Belg* 35: 193-198

**Chambers RE, Bullock DG, Whicher JT** (1989) Urinary total protein estimation-Fact or fiction?. *Nephron* 53: 33-36

**Chen R, Seaton A** (1996) A meta-analysis of mortality among workers exposed to organic solvents. *Occup Med Philadelphia* 46(5): 337-344

**Churchill DN, Fine A, Gault MH** (1983) Association between hydrocarbon exposure and glomerulonephritis. An Appraisal of the evidence. *Nephron* 33: 169-172

**Clearfield HR** (1970) Hepatorenal toxicity from sniffing spot-remover (trichlorethylene). *Am J Digest Dis* 15: 851-856

**Commandeur JN.M, Vermeulen NP.E** (1990) Molecular and biochemical mechanisms of chemically induced nephrotoxicity: a review. *Chem Res Toxicol* 3: 171-194

**Couser WG** (1999) Glomerulonephritis. *Lancet* 353: 1509-1515

**Crisp AJ, Bhalla AK, Hoffbrand BI** (1979) Acute tubular necrosis after exposure to diesel oil. *Brit Med J* 7: 177

**d'Apice AJ.F, Kincaid-Smith P, Becker GJ, Loughhead MG, Freeman JW, Sands JM** (1978) Goodpasture's syndrome in identical twins. *Ann Intern Med* 88(1): 61-62

**Dagg TG, Satin KP, Bailey WJ, Wong O, Harmon LL, Swencicki RE** (1992) An updated cause specific mortality study of petroleum refinery workers. *Brit J Ind Med* 49: 203-212

**Daniell WE, Couser WG, Rosenstock L** (1988) Occupational solvent exposure and glomerulonephritis. A case report and review of the literature, cited in EHC (1996). *J Am Med Assoc (JAMAA)* 259: 2280-2283

**David NJ, Wolman R, Milne FJ, van Niekerk I** (1989) Acute renal failure due to trichloroethylene poisoning. *Brit J Ind Med* 46: 347-349

**De Broe ME, D'Haese P.C., Nuyts GD, Elseviers MM** (1996) Occupational renal diseases. *Curr Opin Nephrol Hypertens* 5: 114-121

**Dekant W, Birner G, Werner M, Parker J** (1998) Glutathione conjugation of perchlorethene in subcellular fractions from rodent and human liver and kidney. *Chem Biol Interact* 116(1-2): 31-43

**Dekant W, Henschler D** (1999) Organ-specific carcinogenicity of haloalkenes mediated by glutathione conjugation. *J Cancer Res Clin Oncol* 125(3-4): 174-181

**Dekant W, Vamvakas S** (1993) V-6 Niere. In: Wichmann HE, Schlipkötter HW, Fülgraff G (ed.) *Handbuch der Umweltmedizin*. Landsberg, ecomed Verlag

**Dekant W, Vamvakas S** (1996) Biotransformation and membrane transport in nephrotoxicity. *Crit Rev Toxicol* 26(3): 309-334

**Delzell E, Austin H, Cole P** (1988) Epidemiologic studies of the petroleum industry. *Occup Med* 3: 455-474

**Di Nucci A, Imbriani M, Ghittori SG, C, Baldi C, Locatelli C, manzo L, Capodaglio E** (1988) 1,2-Dichloropropane-induced liver toxicity: clinical data and preliminary studies in rats. *Arch Toxicol Suppl* 12: 370-374

**Dietrich DR** (1997) Doubting nongenotoxic mechanisms of renal cancer: comparing apples and oranges in the alpha<sub>2</sub>u-globulin hypothesis. *Environ Health Perspect* 105(9): 898-902

**Dietrich DR, Swenberg JA** (1991) NCI-Black-Reiter (NBR) male rats fail to develop renal disease following exposure to agents that induce alpha<sub>2</sub>u-Globulin nephropathy. *Fundam Appl Toxicol* 16: 749-762

**Divine BJ, Barron V, Kaplan SD** (1985) Texaco mortality study. I. Mortality among refinery, petrochemical and research workers. *J Occup Med* 27: 445-447

**Dubach UC, Le Hir M, Gandhi R** (1988) Use of urinary enzymes as markers of nephrotoxicity. *Toxicol Lett* 46: 193-196

**Ehrenreich T** (1977) Renal disease from exposure to solvents. *Ann Clin Lab Sci* 7: 6-16

- Ehrenreich T, Yunis SL, Churg J** (1974) Membranous nephropathy following exposure to volatile hydrocarbons. *Lab Invest* 30: 373
- Elseviers MM, de Broe ME** (1998) Epidemiology of toxic nephropathies. *Adv Nephrol* 27: 241-262
- Endou H** (1998) Recent advances in molecular mechanisms of nephrotoxicity. *Toxicol Lett* 102-103: 29-33
- Essing HG, Schaecke G, Bekmann H, Valentin H, Wittgens H, Weltle D, Rhode D, Pfaeffl A** (1974) Untersuchungen zur Nierenfunktion bei Werkstaettenarbeitern mit langjaehriger Perchloraethylen-Exposition. *Ärztl Dienst* 5(6): 65-72
- Fine LG, Ong AC.M, Norman JT** (1993) Mechanisms of tubulo-interstitial injury in progressive renal diseases. *Eur J Clin Invest* 23: 259-265
- Finn R, Fennerty AG, Ahmad R** (1980) Hydrocarbon exposure and glomerulonephritis. *Clin Nephrol* 14: 173-175
- Fischman CM, Oster JR** (1979) Toxic effects of toluene. A new cause of high anion gap metabolic acidosis. *J Am Med Assoc (JAMAA)* 241(16): 1713-1715
- Franchini I, Cavatorta A, Falzoi M, Lucertini S, Mutti A** (1983) Early indicators of renal damage in workers exposed to organic solvents. *Int Arch Occup Environ Health* 52: 1-9
- Franchini I, Lucertini S, Chiesa E, Mutti A** (1982) Organic solvent exposure and chronic glomerulonephritis: a case-control study. In: X. *Medichem. Paris(U.A.)*, MASSON 169-175
- Frei U, Schober-Halstenberg HJ, QuaSi-Niere Task Group for Quality Assurance in Renal Replacement Therapy** (1999) Annual report of the German renal registry 1998. *Nephrol Dial Transplant* 14: 1085-1090
- Friedman EA, Greenberg JB, Merrill JP.D, G.J** (1962) Consequences of ethylene glycol poisoning. *Am J Med* 32: 891-902
- Geiling EM.K, Cannon PR** (1938) Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning. *J Am Med Assoc (JAMAA)* 111(10): 919-926
- Gérin M, Patrice S, Begin D, Goldberg MS, Vyskocil A, Adib G, Drolet D, Viau C** (1997) A study of ethylene glycol exposure and kidney function of aircraft de-icing workers. *Int Arch Occup Environ Health* 69(4): 255-265
- Giersiepen K, Straif K** (1992) Organische Loesungsmittel am Arbeitsplatz und Nierenschaeden: Aktueller Kenntnisstand und zukuenftige Perspektiven. *Arbeitsmed Sozialmed Präventivmed* 27: 504-506
- Glaeser JA** (1892) III. Zwei Fälle von Nephritis acuta ex intoxicatione (?). *Klin Med* 21: 388-390

- Goldstein RS, Kuo CH, Hook JB** (1990) Biochemical mechanisms of xenobiotic-induced nephrotoxicity. In: Goldstein RS, Hewitt WR, Hook JB (ed.) Toxic interactions, Part III: Alteration of chemically induced nephrotoxicity. San Diego, Ca, USA, Academic Press 261-298
- Goldstein RS, Schnellmann RG** (1996) Toxic responses of the kidney. In: Klaassen CD, Amdur MO, Doull J (ed.) Casarett and Doull's Toxicology - The Basic Science of Poisons (Fifth Edition). New York, USA, McGraw-Hill, Health Professions Division 417-433
- Gregorini G, Farioli A, Donato F, et al.** (1993) Association between silica exposure and necrotizing crescentic glomerulonephritis with P-ANCA and anti-MPO antibodies: A hospital-based case-control study. *Adv Exp Med Biol* 336: 435-439
- Guder WG** (1987) 4.4. Niere und ableitende Harnwege. In: Greiling H, Gressner AM (ed.) Lehrbuch der klinischen Chemie und Pathobiochemie. Stuttgart, New York, Schattauer
- Gutch CF, Tomhave WG, Stevens SC** (1965) Acute renal failure due to inhalation of trichloroethylene. *Ann Intern Med* 63: 128-134  
**Hanis NM, Shallenberger LG, Donaleski DL, Sales EA** (1985) A retrospective cohort mortality study of workers in three major U.S. refineries and chemical plants. Part I, comparisons with U.S. population. *J Occup Med* 27: 283-292
- Harrington JM, Whitby H, Gray CN, Reid FJ, Caw T, Waterhouse JA** (1989) Renal disease and occupational exposure to organic solvents: a case referent approach. *Brit J Ind Med* 46: 643-650
- Harrison DJ, Thomson D, Macdonald MK** (1986) Membranous glomerulonephritis. *J Clin Pathol* 39: 167-171
- Hashimoto DM, Kelsey KT, Seitz T, Feldman HA, Yakes B, Christiani DC** (1991) The presence of urinary cellular sediment and albuminuria in newspaper pressworkers exposed to solvents. *J Occup Med* 33: 516-526
- Haufroid V, Thirion F, Mertens P, Buchet JP, Lison D** (1997) Biological monitoring of workers exposed to low levels of 2-butoxyethanol. *Int Arch Occup Environ Health* 70(4): 232-236
- Hawksworth GM, McCarthy R, McGoldrick T, Stewart V, Tisocki K, Lock EA** (1996) Site specific drug and xenobiotic induced renal toxicity. *Arch Toxicol Suppl* 18: 184-192
- Heaf J, Lokkegaard H, Larsen S** (1999) The epidemiology and prognosis of glomerulonephritis in Denmark 1985-1997. *Nephrol Dial Transplant* 14: 1889-1897
- Heale WF, Matthiesson AM, Niall JF** (1969) Lung haemorrhage and nephritis (Goodpasture's syndrome). *Med J Aust* iii: 355-357

- Hearne FT, Pifer JW, Grose F** (1990) Absence of adverse mortality effects in workers exposed to methylene chloride: an update. *J Occup Med* 32: 234-240
- Hörl WH** (1998) 23.2 Diagnostische Verfahren. In: Classen M, Diehl V, Kochsiek K (ed.) *Innere Medizin*. Münschen, Urban, Schwarzenberg
- Hotz P** (1994) Occupational hydrocarbon exposure and chronic nephropathy. *Toxicology* 90: 163-283
- Hotz P, Boillat MA** (1989) Kohlenwasserstoffe und nichtneoplastische Nierenkrankheiten. *Ther Umsch* 46: 801-808
- Hotz P, Carbonnelle P, Tschopp A, Rousseau O, Bernard A** (1997) Assessment for subclinical kidney damage in workers exposed to low concentrations of hydrocarbons. *Int J Occup Environ Health* 3: 266-272
- Hotz P, Gonzalez-Lorenzo J, Siles E, Trujillano G, Lauwerys R, Bernard A** (1995) Subclinical signs of kidney dysfunction following short exposure to silica in the absence of silicosis. *Nephron* 70: 438-442
- Hotz P, Pilliod J, Bernard A, Berode M, Rey F, Mazzocato C, Guillemin M, Boillat MA** (1990) Hydrocarbon exposure, hypertension and kidney function tests. *Int Arch Occup Environ Health* 62: 501-508
- Hotz P, Pilliod J, Söderström D, Rey F, Boillac MA, Savolainen H** (1989) Relationships between renal function tests and a retrospective organic solvent exposure score. *Brit J Ind Med* 46: 815-819
- Hotz P, Thielemans N, Bernard A, Gutzwiller F, Lauwerys R** (1993) Serum laminin, hydrocarbon exposure, and glomerular damage. *Brit J Ind Med* 50: 1104-1110
- Ibels LS, Györy AZ** (1994) IgA Nephropathy: Analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine* 73(2): 79-102
- Jacobson HR** (1991) Chronic renal failure: pathophysiology. *Lancet* 338: 419-423
- Janssen S, van der Geest S, Meijer S, Uges DR.A** (1988) Impairment of organ function after oral ingestion of refined petrol. *Intensive Care Med* 14: 238-240
- Johanson G, Boman A** (1991) Percutaneous absorption of 2-butoxyethanol vapour in human subjects. *Brit J Ind Med* 48: 788-792
- Johnstone RT** (1959) Death due to dioxane?. *Arch Industr Hyg* 20: 445-447
- Jonker D, Woutersen RA, Feron VJ** (1996) Toxicity of mixtures of nephrotoxicants with similar or dissimilar mode of action. *Food Chem Toxicol* 34(11-12): 1075-1082
- Jung K** (1991) Enzyme activities in urine: how should we express their excretion? A critical literature review. *Eur J Clin Chem Clin Biochem* 29: 725-729

- Jung K, Hempel A, Grützmann K-D, Hempel RD, Schreiber G** (1990) Age-dependent excretion of alamine aminopeptidase, alkaline phosphatase, gamma-glutamyltransferase and N-acetyl-beta-D-glucosaminidase in human urine. *Enzyme* 43: 10-16
- Jungers P, Chauveau P, Descamps-Latscha B, Labrunie M, Giraud E, Man NK, Grünfeld JP, Jacobs C** (1996) Age and gender-related incidence of chronic renal failure in a french urban area: a prospective epidemiologic study. *Nephrol Dial Transplant* 11: 1542-1546
- Kannel WB, Stampfer MJ, Castelli WP, Verter J** (1984) The prognostic significance of proteinuria: The Framingham study. *Am Heart J* 108: 1347-1352
- Kaplan SD** (1986) Update of a mortality study of workers. *J Occup Health* 28: 514-516
- Keller F, Nekarda H** (1985) Fatal relapse in Goodpastur's syndrome 3 years after plasma exchange. *Respiration* 48: 62-66
- Keogh AM, Ibels LS, Allen DH, Isbester JP** (1984) Exacerbation of Goodpasture's syndrome after inadvertent exposure to hydrocarbon fumes. *Brit Med J* 288: 188
- Klavis G, Drommer W** (1970) Goodpasture-Syndrome und Benzineinwirkung. *Arch Toxikol* 26: 40-55
- Kleinknecht D, Morel-Maroger L, Callard P, Adhémar JP, Mahieu P** (1980) Antiglomerular basement membrane nephritis after solvent exposure. *Arch Int Med* 140: 230-232
- Kluwe WM** (1981) The nephrotoxicity of low molecular weight halogenated alkane solvents, pesticides, and chemical intermediates. In: Hook JB (ed.) *Toxicology of the kidney. Target organ toxicology series*. New York, Raven Press 179-226
- Kraemmer Nielsen H, Krusell L, Baelum J, Lundqvist G, Omland O, Vaeth M, Husted SE, Mogensen CE, Geday E** (1985) Renal effects of acute exposure to toluene. *Acta med Scand* 218: 317-321
- Kreienbrock L, Schach S** (1997) *Epidemiologische Methoden*. Stuttgart, Jena, Lübeck, Ulm, Gustav Fischer
- Krusell, Nielsen HK, Baelum J, Lundqvist G, Omland O, Vaeth M, Husted SE, Mogensen CE, Geday E** (1985) Renal effects of chronic exposure to organic solvents: a clinical controlled trial. *Acta med Scand* 218: 323-327
- Lagrue G** (1976) Hydrocarbon exposure and chronic glomerulonephritis. *Lancet* 1: 1191
- Lagrue G, Kamalodine T, Hirbec G, Bernaudin JF, Guerrero J, Zhepova F** (1977) Role de l'inhalation de substances toxiques dans la genese des glomerulonephrites. *Nouv Press Med* 6(39): 3609-3613

- LaKind JS, McKenna EA, Hubner RP, Tardiff RG** (1999) A review of the comparative mammalian toxicity of ethylene glycol and propylene glycol. *Crit Rev Toxicol* 29(4): 331-365
- Landry JF, Langlois S** (1998) Acute exposure to aliphatic hydrocarbons: An unusual cause of acute tubular necrosis. *Arch Int Med* 158(16): 1821-1823
- Lauwerys R, Bernard A** (1989) Preclinical detection of nephrotoxicity: description of the tests and appraisal of their health significance. *Toxicol Lett* 46: 13-29
- Lauwerys R, Bernard A, Cardenas A** (1992) Monitoring of early nephrotoxic effects of industrial chemicals. *Toxicol Lett* 64/65: 33-42
- Lauwerys R, Bernard A, Viau C, Buchet JP** (1985) Kidney disorders and hematotoxicity from organic solvent exposure. *Scand J Work Environ Health Suppl* 11: 83-90
- Lison AE** (1989) Early detection of renal dysfunction: practical recommendations. *Toxicol Lett* 46: 251-255
- Lock EA** (1988) Studies on the mechanism of nephrotoxicity and nephrocarcinogenicity of halogenated alkenes. *CRC Crit Rev Toxicol* 19: 23-42
- Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney AP.S, Briggs D, McCredie M, Boyle P** (2000) Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: Results from an international comparative study. *Am J Kidney Dis* 35(1): 157-165
- Marcussen N, Olsen S, Larsen S, Starklint H, Thomsen OF** (1995) Reproducibility of the WHO classification of glomerulonephritis. *Clin Nephrol* 44(4): 220-224
- Marjot R, McLeod AA** (1989) Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 8: 301-306
- McCarthy RI, Lock EA, Hawksworth GM** (1994) Cytosolic C-S lyase activity in human kidney samples - relevance for the nephrotoxicity of halogenated alkenes in man. *Toxicol Ind Health* 10(1-2): 103-112
- Melnick RL, Kohn MC** (1999) Possible mechanisms of inductions of renal tubule cell neoplasms in rats associated with alpha(2u)-globulin: role of protein accumulation versus ligand delivery to the kidney. *Int Agency Res Cancer Sci Pub* 147: 119-137
- Metcalf PA, Baker JR, Scragg RK.R, Dryson E, Scott AJ, Wild CJ** (1993) Albuminuria in people at least 40 years old: Effect of alcohol consumption, regular exercise, and cigarette smoking. *Clin Chem* 39(9): 1793-1797
- Meyer BR, Fischbein A, Rosenman K, Lerman Y, Drayer DE, Reidenberg MM** (1984) Increased urinary enzyme excretion in workers exposed to nephrotoxic chemicals. *Am J Med* 76(6): 989-998

**Miller L, Pateras V, Friederici H, Engel G** (1985) Acute tubular necrosis after inhalation exposure to methylene chloride. *Arch Int Med* 145: 145-146

**Morgan RW, Kaplan SD, Gaffey WR** (1981) A general mortality study of production workers in the paint and coatings manufacturing industry. *J Occup Med* 23(1): 13-21

**Morley R, Eccleston DW, Douglas CP, Greville WE.J, Scott DJ, Anderson J** (1970) Xylene poisoning: a report on one fatal case and two cases of recovery after prolonged unconsciousness. *Brit Med J* 3: 442-443

**Mueller, Price RG, Porter GA** (1997) Proceedings of the joint US/EU workshop: urinary biomarkers to detect significant effects of environmental and occupational exposure to nephrotoxins. *Ren Fail* 19(4): 501-504

**Mullin LS, Ader AW, Daughtrey WC, Frost DZ, Greenwood MR** (1990) Toxicology update isoparaffinic hydrocarbons: A summary of physical properties, toxicity studies and human exposure. *J Appl Toxicol* 10: 135-142

**Mutti A** (1989) Detection of renal disease in humans: developing markers and methods. *Toxicol Lett* 46(1-3): 177-191

**Mutti A** (1996) Organic solvents and the kidney. *J Occup Health* 38: 162-169

**Mutti A** (1999) Biological monitoring in occupational and environmental toxicology. *Toxicol Lett* 108: 77-89

**Mutti A, Alinovi R, Bergamaschi E, Biagini C, Cavazzini S, Franchini I, Lauwerys RR, Bernard AM, Roels H, Gelpi E, Rosello J, Ramis I, Price RG, Taylor SA, De Broe M, Nuyts GD, Stolte H, Fels LM, Herbort C** (1992) Nephropathies and exposure to perchloroethylene in dry-cleaners. *Lancet* 340: 189-193

**Mutti A, Coccini T, Alinovi R, Toubeau G, Broeckaert F, Bergamaschi E, Mozzoni PN, D, Bernard A, Manzo L** (1999) Exposure to hydrocarbons and renal disease: an experimental animal model. *Ren Fail* 21(3-4): 369-385

**Mutti A, Lucertini S, Falzoi M, Cavatorta A, Franchini I** (1981) Organic solvents and chronic glomerulonephritis: A cross-sectional study with negative finding for aliphatic and alicyclic C5-C7 hydrocarbons. *J Appl Toxicol* 1: 224-226

**Nagaya T, Ishikawa N, Hata H** (1989) Urinary total protein and beta-2-microglobulin in workers exposed to trichlorethylene. *Environ Res* 50: 86-92

**Nagelkerke JF, Boogaard PJ** (1991) Nephrotoxicity of halogenated alkenyl cysteine-S-conjugates. *Life Sci* 49: 1769-1776

**Narvarte J, Saba SR, Ramirez G** (1989) Occupational exposure to organic solvents causing chronic tubulointerstitial nephritis. *Arch Int Med* 149: 154-158

**Nath KA** (1992) Tubulointerstitial changes as a major determinant in the progression of renal damage. *Am J Kidney Dis* 20(1): 1-17



- Nathan AW, Toseland PA** (1979) Goodpasture's syndrome and trichloroethane intoxication. *Brit J Clin Pharmacol* 8: 284-286
- Nelson DI, Nelson RY, Hart KJ, Asal NR** (1995) Hydrocarbon exposure assessment methodology for an epidemiologic study of renal disease. *Appl Occup Environ Hyg* 10(4): 299-310
- Nelson NA, Robins TG, Port FK** (1990) Solvent nephrotoxicity in humans and experimental animals. *Am J Nephrol* 10: 10-20
- Newman DJ, Pugia MJ, Lott JA, Wallace JF, Hiar AM** (2000) Urinary protein and albumin excretion corrected by creatinine and specific gravity. *Clin Chem Acta* 294(1-2): 139-155
- Ng TP, Ng YL, Lee HS et al.** (1992) A study of silica nephrotoxicity in exposed silicotic and non-silicotic workers. *Br J Ind Med* 49:35-37
- Ng TP, Ong SG, Lam WK, Jones MG, Cheung CK, Ong CN** (1990) Urinary levels of proteins and metabolites in workers exposed to toluene. *Int Arch Occup Environ Health* 62: 43-46
- Nitter-Hauge S** (1970) Poisoning with ethylene glycol monomethyl ether. *Acta med Scand* 188: 277-280
- Normand JC, Bernard A, Buchet JP, Prost G, Lauwerys R** (1989) Biométrie rénale de l'exposition chronique aux solvants. Résultats préliminaires d'une enquête épidémiologique transversale dans l'industrie de la peinture. *Arch Mal Prof* 50: 244-245
- Normand JC, Bernard A, Buchet JP, Roels H, Michaux J, De Wandeler V, Lauwerys R** (1990) Recherche d'anomalies rénales infracliniques chez les travailleurs de deux entreprises productrices de peintures. *Arch Mal Prof Med Travail Sec Soc* 51(4): 261-266
- Nuyts GD, Elseviers MM, De Broe ME** (1989) Health impact of renal disease due to nephrotoxicity. *Toxicol Lett* 46: 31-44
- Nuyts GD, van Vlem E, Thys J, de Leersnijder D, d'Haese PC, Elseviers MM, de Broe ME** (1995) New occupational risk factors for chronic renal failure. *Lancet* 346: 7-11
- Olmstead EV, Flemington NJ** (1960) Pathological changes in ethylene dibromide poisoning. *Arch Industr Health* 21: 525-529
- Osterloh JD, Feldmann BJ** (1993) Urinary protein markers in pesticide applicators during a chlorinated hydrocarbon exposure. *Environ Res* 63: 171-181
- Pähler A., Parker J, Dekant W** (1999) Dose-dependent protein adduct formation in kidney, liver, and blood of rats and in human blood after perchloroethene inhalation. *Toxicol Sci* 48: 5-13

**Pai P, Bone JM, Bell GM** (1998) Hydrocarbon exposure and glomerulonephritis due to systemic vasculitis. *Nephrol Dial Transplant* 13(5): 1321-1323

**Pai P, Hindell P, Stevenson A, Mason H, Bell GM** (1996) Occupational hydrocarbon (HC) exposure and nephrotoxicity. *J Am Soc Nephrol* 7: 1340

**Pai P, Hindell P, Stevenson A, Mason H, Bell GM** (1997) Genetic variants of microsomal metabolism and susceptibility to hydrocarbon-associated glomerulonephritis. *QJM* 90(11): 693-698

**Pai P, Stevenson A, Mason H, Bell GM** (1998) Occupational hydrocarbon exposure and nephrotoxicity: a cohort study and literature review. *Postgrad Med J* 74(870): 225-228

**Park RM, Silverstein MA, Green MA, Mirer FE** (1990) Brain cancer mortality at a manufacturer of aerospace electromechanical systems. *Am J Ind Med* 17: 537-552

**Patel R, Benjamin JJ** (1986) Renal disease associated with toluene inhalation. *J Toxicol /Clin Toxicol* 24: 213-223  
**Pederen LM** (1987) Biological studies in human exposure to and poisoning with organic solvent. *Pharmacol Toxicol* 3: 1-38

**Pedersen LM, Rasmussen JM** (1982) The haematological and biochemical pattern in occupational organic solvent poisoning and exposure. *Int Arch Occup Environ Health* 51: 113-126

**Phillips SC, Petrone RL, Hemstreet GP.III** (1988) 8. A review of the non-neoplastic kidney effects of hydrocarbon exposure in humans. *Occup Med* 3: 495-509

**Piscator M** (1989) Markers of tubular dysfunction. *Toxicol Lett* 46: 197-204

**Porro A, Lomonte C, Coratelli P, Passavanti G, Ferri GM, Assennato G** (1992) Chronic glomerulonephritis and exposure to solvents: A case-referent study. *Brit J Ind Med* 49: 738-742

**Port FK** (1993) Worldwide demographics and future trends in end-stage renal disease. *Kidney Int Suppl* 43(S41): S4-S7

**Pozzi C, Marai P, Ponti R, Dell'Oro C, Sala C, Zedda S, Locatelli F** (1985) Toxicity in man due to stain removers containing 1,2-dichloropropane. *Brit J Ind Med* 42: 770-772

**Price RG** (1982) Urinary enzymes, nephrotoxicity and renal disease. *Toxicology* 23: 99-134

**Price RG** (1992) The role of NAG in the diagnosis of kidney disease including the monitoring of nephrotoxicity. *Clin Nephrol* 38/Sup.1: S14-S19

**Price RG** (2000) Urinalysis to exclude and monitor nephrotoxicity. *Clin Chem Acta* 297: 173-182

**Price RG, Berndt WO, Finn WF, Aresini G, Manley SE, Fels LM, Shaikh ZA, Mutti A** (1997) Urinary biomarkers to detect significant effects of environmental and occupational exposure to nephrotoxins. III. Minimal battery of tests to assess subclinical nephrotoxicity for epidemiological studies based on current knowledge. *Ren Fail* 19(4): 535-552

**Price RG, Taylor SA, Chivers I, Arce Tomas M, Crutcher E, Franchini .I, Alinovi R, Cavazzini S, Bergamschi E, Mutti A, Vettori MV, Lauwerys R, Bernard A, Kabanda A, Roels H, Thielemanns N, Hotz P, De Broe ME, Elseviers MM, Nuyts GD, Gelpi E, Hotter G, Rosello JR, I, Stolte H, et al.** (1996) Development and validation of new screening tests for nephrotoxic effects. *Hum Exp Toxicol* 15 S1: 10-19

**Price RG, Taylor SA, Crutcher E, Bergamschi E, Franchini I, Mackie AD** (1995) The assay of laminin fragments in serum and urine as an indicator of renal damage by toxins. *Toxicol Lett* 77(1-3): 313-318

**Price RG, Taylor SA, Crutcher E.** (1994) Assay of laminin fragments in the assessment of renal disease. *Kidney Int Suppl* 46 S47: S25-S28

**Raphael K** (1987) Recall bias: A proposal for assessment and control. *Int J Epidemiol* 16(2): 167-170

**Rasmussen K, Brogren CH, Sabroe S** (1993) Subclinical affection of liver and kidney function and solvent exposure. *Int Arch Occup Environ Health* 64: 445-448

**Ravnskov U** (1977) Exposure to organic solvents in acute post-streptococcal glomerulonephritis. *Lancet* 2: 258

**Ravnskov U** (1978) Exposure to organic solvents- a missing link in poststreptococcal glomerulonephritis?. *Acta med Scand* 203: 351-356

**Ravnskov U** (1979) Acute glomerulonephritis and exposure to organic solvents in father and daughter. *Acta med Scand* 205: 581-582

**Ravnskov U** (1986) Influence of hydrocarbon exposure on the course of glomerulonephritis. *Nephron* 42: 156-160

**Ravnskov U** (1989) Non-systemic glomerulonephritis: exposure to nephro- and immunotoxic chemicals predispose to immunologic harassment. *Med Hypotheses* 30: 115-122

**Ravnskov U** (1990) Glomerulonephritis, renal carcinoma and solvent exposure: bias from choice of referents (letter). *Brit J Ind Med* 47: 791-792

**Ravnskov U** (1992) Hydrocarbons and renal failure: primary damage in glomerulonephritis is tubular, not glomerular. *Nephron* 61: 243

**Ravnskov U** (1998) The subepithelial formation of immune complexes in membranous glomerulonephritis may be harmless and secondary to toxic or allergic factors. *Scand J Immun* 48: 469-474

**Ravnskov U** (2000) Hydrocarbons may worsen renal function in glomerulonephritis: a meta-analysis of the case-control studies. *Am J Ind Med* 37: 599-606

**Ravnskov U, Forsberg B** (1979) Improvement of glomerulonephritis after discontinuation of solvent exposure. *Lancet* 1: 1194

**Ravnskov U, Forsberg B, Skerfving S** (1979) Glomerulonephritis and exposure to organic solvents. A case-control study. *Acta med Scand* 205: 575-579

**Ravnskov U, Lundström S, Norden A** (1983) Hydrocarbon exposure and glomerulonephritis: Evidence from patients' occupations. *Lancet* 2: 1214-1216

**Reidenberg MM, Powers DV, Sevy RW, Bello CT** (1964) Acute renal failure due to nephrotoxins. *Am J Med Sci* 247: 25-29

**Rheinhard** (1887) Ein Fall von Terpentintoxication in Folge Einathmens von Terpentinoel. *Dtsch Med Wochenschr* 13: 256

**Ridder** (1923) Terpentinoelvergiftung mit Nierenschaedigung durch aeusserliche Anwendung des Oels. *Dtsch Med Wochenschr* 2: 1369

**Ridder GM, von Bargaen EC, Alden CL, Parker RD** (1990) Increased hyaline droplet formation in male rats exposed to decalin is dependent on the presence of a<sub>2u</sub>-globulin. *Fundam Appl Toxicol* 15: 732-743

**Robert R, Touchard G, Meurice JC, Pourrat O, Yver L** (1988) Severe Goodpasture's syndrome after glue sniffing. *Nephrol Dial Transplant* 3: 483-484

**Rocskay AZ, Robins TG, Schork MA, Echeverria D, Proctor SP, White RF** (1993) Renal effects of naphtha exposure among automotive workers. *J Occup Med* 35: 617-622

**Rodgers IS, Baetcke KP** (1993) Interpretation of male rat renal tubule tumors. *Environ Health Perspect Suppl* 101(6): 45-52

**Rosenman KD, Moore-Fuller M, Reilly MJ** (2000) Kidney disease and silicosis. *Nephron* 85(1): 14-19

**Roy AT, Brautbar N, Lee DB.N** (1991) Hydrocarbons and renal failure. *Nephron* 58: 385-392

**Rushton L** (1993) Further follow up of mortality in a United Kingdom oil distribution centre cohort. *Brit J Ind Med* 50: 561-569

**Rushton L, Alderson MR** (1981) An epidemiological survey of eight oil refineries in Britain. *Brit J Ind Med* 38: 225-234  
**Rushton L, Alderson MR** (1983) Epidemiological survey of oil distribution centres in Britain. *Brit J Ind Med* 40: 330-339

**Saland G** (1967) Accidental exposure to perchloroethylene. *N Y State J Med* 67: 2359-2361

**Schena FP, Italian Group of Renal Immunopathology** (1997) Survey of the Italian registry of renal biopsies. Frequency of the renal diseases for 7 consecutive years. *Nephrol Dial Transplant* 12: 418-426

**Schenker MB, Jacobs JA** (1996) Respiratory effects of organic solvent exposure. *Tuber Lung Dis* 77(1): 4-18

**Seldén A, Hultberg B, Ulander A, Ahlborg G, Jr** (1993) Trichlorethylene exposure in vapour degreasing and the urinary excretion of N-acetyl-beta-D-glucosaminidase. *Arch Toxicol* 67: 224-226

**Sesso R, Stolley PD, Salgado N, Pereira AB, Ramos OL** (1990) Exposure to hydrocarbons and rapidly progressive glomerulonephritis. *Braz J Med Biol Res* 23: 225-233

**Seymour AE** (1985) Glomerulonephritis: approaches to classification. *Pathol* 17: 225-238

**Solet D, Robins TG** (1991) Renal function in dry cleaning workers exposed to perchloroethylene. *Am J Ind Med* 20(5): 601-614

**Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN, Cohen JL** (1991) Retrospective cohort mortality study of workers at an aircraft maintenance facility. I Epidemiological results. II Exposures and their assessment. *Brit J Ind Med* 48: 515-530

**Steenland NK, Thun MJ, Ferguson BA, Port FK** (1990) Occupational and other exposures associated with male end-stage renal disease: a case control study. *Am J Public Health* 80(2): 153-156

**Stengel B, Cénée S, Limasset JC, Diebold F, Michard D, Druet P, Hémon D** (1998) Immunologic and renal markers among photogravure printers exposed to toluene. *Scand J Work Environ Health* 24(4): 276-284

**Stengel B, Cenee S, Limasset JC, Protois JC, Marcelli A, Brochard P., Hemon D.** (1995) Organic solvent exposure may increase the risk of glomerular nephropathies with chronic renal failure. *Int J Epidemiol* 24: 427-434

**Stengel B, Cenee S, Limasset JC, Protois JC, Marcelli A, Hemon D** (1996) Nephropathies glomerulaires et exposition aux solvants organique - etudes cas-temoins. *Bull Acad Nat Med* 180(4): 871-883

**Stengel B, Watier L, Chouquet C, Cénée S, Philippon C, Hémon D** (1999) Influence of renal biomarker variability on the design and interpretation of occupational or environmental studies. *Toxicol Lett* 106 (1): 69-77

**Stevenson A, Yaqoob M, Mason H, Pai P, Bell GM** (1995) Biochemical markers of basement membrane disturbances and occupational exposure to hydrocarbons and mixed solvents. *QJM* 88: 23-28

**Swenberg JA, Lehman-McKeeman LD** (1999) Alpha-urinary globulin-associated nephropathy as a mechanism of renal tubule cell carcinogenesis in male rats. *Int Agency Res Cancer Sci Pub* 147: 95-118

**Taher SM, Anderson RJ, McCartney R, Popovtzer MM, Schrier RW** (1974) Renal tubular acidosis associated with toluene "sniffing". *New Engl J Med* 290: 765-768

**Taylor SA, Chivers ID, Price RG, Arce Thomas M, Milligan P, Francini I, Alinovi R, Cavazzini S, Bergamaschi E, Vittori M, Mutti A, Lauwerys RR, Bernard AM, Roels HA, De Broe ME, Nuyts GD, Elsviers MM, Hotter G, Ramis I, Rosello J, Gelpi E, Stolte H, Eisenberger U, Fels LM** (1997) The assessment of biomarkers to detect nephrotoxicity using an integrated database. *Environ Res* 75(1): 23-33

**Teschner M, Heidland A** (1998) Akutes Nierenversagen. In: Classen M, Diehl V, Kochsiek K (ed.) *Innere Medizin*. München, Urban, Schwarzenberg

**Thews G, Mutschler E, Vaupel P** (1991) *Anatomie, Physiologie, Pathophysiologie des Menschen*. Stuttgart, Wissenschaftliche Verlagsgesellschaft mgH

**Thomas L** (1998a) 12.1 Clinical laboratory diagnosis of kidney and urinary tract disorders. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 362-366

**Thomas L** (1998b) 12.2 Creatinine. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 366-371

**Thomas L** (1998c) 12.3 Creatinine clearance. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 371-374

**Thomas L** (1998d) 12.5 Erythrocytes, leukocytes, and casts in the urine. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 377-382

**Thomas L** (1998e) 18.14  $\beta_2$ -microglobulin. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 685-688

**Thomas L** (1998g) 18.14 Inflammatory reaction. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 689-697

**Thomas L** (1998h) 18.8 Cystatin C. In: Thomas L (ed.) *Clinical laboratory diagnostics*. Frankfurt, TH-Books Verlagsgesellschaft 662-663

**Triebig G, Blume J** (1992) Organische Lösungsmittel am Arbeitsplatz und Nierenschäden: Aktueller Kenntnisstand und zukünftige Perspektiven. *Arbeitsmed Sozialmed Präventivmed* 27: 190-199

**US EPA** (1991) Alpha 2<sub>μ</sub>-globulin association with chemically induced renal toxicity and neoplasia in the rat. Risk Assessment Forum. EPA/625/3-91/019 F. US EPA, Washington DC.

**Vamvakas S, Bruning T, Bolt HM, Henschler D, Ulm K** (2000) Renal-cell cancer correlated with occupational exposure to trichloroethene. *J Cancer Res Clin Oncol* 126(3): 178-180

**Van der Laan G** (1980) Chronic glomerulonephritis and organic solvents. *Int Arch Occup Environ Health* 47: 1-8

**Verplanke AJ, Herner RF** (1998) Effects on the kidney of occupational exposure to styrene. *Int Arch Occup Environ Health* 71 (1): 47-52

**Verplanke AJ, Leummens MH, Herber RF** (1999) Occupational exposure to tetrachloroethene and its effects on the kidneys. *J Occup Environ Med* 41(1): 11-16

**Viau C, Bernard A, Lauwerys R, Buchet JP, Quaeghebeur L, Cornu ME, Phillips SC, Mutti A, Lucertini S, Franchini I** (1987) A cross-sectional survey of kidney function in refinery employees. *Am J Ind Med* 11: 177-187

**Völkel W, Friedwald M, Lederer E, Pähler A, Parker J, Dekant W** (1998) Biotransformation of perchloroethene: dose-dependent excretion of trichloroacetic acid, dichloroacetic acid, and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. *Toxicol Appl Pharmacol* 153(1): 20-27

**von Oettingen WF** (1937) The halogenated hydrocarbons: their toxicity and potential dangers. *J Ind Hyg Toxicol* 19(8): 349-448

**von Scheele C, Althoff P, Kempf V, Schelin U** (1976) Nephrotoxic syndrome due to subacute glomerulonephritis - Association with hydrocarbon exposure?. *Acta med Scand* 200: 427-429

**Vyskocil A, Popler A, Skutilova I, Ciharova M, Ettlerova E, Lauwerys RR, Bernard AM** (1991) Urinary excretion of proteins and enzymes in workers exposed to hydrocarbons in a shoe factory. *Int Arch Occup Environ Health* 63: 359-362

**Wakai K, Kawamura T, Matsuo S, Hotta N, Ohno Y** (1999) Risk factors for IgA nephropathy: a case control study in Japan. *Am J Kidney Dis* 33(4): 738-745

**Walser M** (1990) Progression of chronic renal failure in man. *Kidney Int* 37: 1195-1210

**Walser M, Drew HH, Lafrance ND** (1988) Creatinine measurements often yield false estimates of progression in chronic renal failure. *Kidney Int* 34: 412-418

**Watts GF, Morris RW, Khan K, Polak A** (1988) Urinary albumin excretion in healthy adult subjects: reference values and some factors affecting their interpretation. *Clin Chim Acta* 172: 191-198

**Wedeen RP** (1992) Renal diseases of occupational origin. *Occup Med* 7: 449-463

**Whitworth JA, Lawrence JR, Meadows R** (1974) Goodpasture's syndrome. A review of nine cases and an evaluation of therapy. *Aust N Z J Med* 4: 167-177

**Wong O** (1990) A cohort mortality study and a case-control study of workers potentially exposed to styrene in the reinforced plastics and composites industry. *Brit J Ind Med* 47: 753-762

**Yaqoob M, Bell GM** (1994) Occupational factors and renal disease. *Ren Fail* 16/4: 425-434

**Yaqoob M, Bell GM, Percy DF, Finn R** (1992) Primary glomerulonephritis and hydrocarbon exposure: A case-control study and literature review. *QJM* 83: 409-418

**Yaqoob M, Bell GM, Stevenson A, Mason H, Percy DF** (1993) Renal impairment with chronic hydrocarbon exposure. *QJM* 86: 165-174

**Yaqoob M, King A, McClelland P, McDicken I, Bell GM** (1994) Relationship between hydrocarbon exposure and nephropathology in primary glomerulonephritis. *Nephrol Dial Transplant* 9: 1575-1579

**Yaqoob M, Patrick AW, McClelland P, Stevenson A, Mason H, Percy DF, White MC, Bell GM** (1994) Occupational hydrocarbon exposure and diabetic nephropathy. *Diabet Med* 11: 789-793

**Yodaiken RE, Babcock JR** (1973) 1,2-Dichloroethane poisoning. *Arch Environ Health* 26: 281-284

**Zimmerman SW, Groehler K, Beirne GJ** (1975) Hydrocarbon exposure and chronic glomerulonephritis. *Lancet* 2: 199-201

**Zschiesche W, Triebig G** (1990) Untersuchung von Nierenfunktionsparametern bei langjaehrig loesungsmittlexponierten Malern und Spritzlackierern. *Arbeitsmed Sozialmed Präventivmed* 25: 259-263



## **9 Annex**

### **9.1 Tables of values of biological effect monitoring parameters**

| Main compounds    | Concentration (mg/m <sup>3</sup> ) |          | Albumin (mg/g creatinine) |                                  |                                   |                      |                                  |                                   | Remarks  | Reference                   |
|-------------------|------------------------------------|----------|---------------------------|----------------------------------|-----------------------------------|----------------------|----------------------------------|-----------------------------------|--|-----------------------------|
|                   |                                    |          | Exposed workers           |                                  |                                   | Non-exposed controls |                                  |                                   |  |                             |
|                   | TWA                                | Range    | No.                       | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)                 | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)                 |  |                             |
| Toluene, methanol |                                    |          | 245                       | 5.3 <sup>g,7</sup>               | 4.6 <sup>7</sup><br>(0.18 – 1003) | 67                   | 4.4 <sup>7</sup>                 | 4.0 <sup>7</sup><br>(0.27 – 31.8) | Exposure scores, not related to lifetime exposure, present occupation or exposure duration | HOTZ et al. (1990)          |
| Toluene, xylene   | ca. 95<br>(toluene) <sup>2</sup>   |          | 118                       | ca. 5 <sup>g</sup>               |                                   | 80                   | ca. 5 <sup>g</sup>               |                                   | Values estimated from figures  | FRANCHINI et al. (1983)     |
| Toluene           | 141                                |          | 92                        | 4.9 <sup>g</sup><br>(GSD 19.7)   |                                   | 74                   | 5.0 <sup>g</sup><br>(GSD 18.8)   |                                   |  | STENGEL et al. (1998)       |
| Toluene           | < 380 <sup>2</sup>                 |          | 45                        |                                  | 10.6<br>(2.6 – 577.0)             | 45                   |                                  | 11.5<br>(4.4 – 55.7)              |  | NG et al. (1990)            |
| Styrene           | 113                                |          | 5                         | 1.85 <sup>g</sup>                |                                   | 5                    | 1.28 <sup>g</sup>                |                                   | Overnight urine samples  | VERPLANKE and HERBER (1998) |
|                   |                                    |          | 5                         | 4.03 <sup>g</sup>                |                                   | 5                    | 2.33 <sup>g</sup>                |                                   | End-of-shift-samples; 2 exp./0 controls > upper ref. limit of 20 mg/g creat.               |                             |
| Styrene           | ca. 215 <sup>2</sup>               |          | 51                        | ca. 5 <sup>g</sup>               |                                   | 80                   | ca. 5 <sup>g</sup>               |                                   | Values estimated from figures  | FRANCHINI et al. (1983)     |
| Styrene           | 225                                | 83 – 366 | 37                        | 12.8 <sup>g</sup>                | (5.4 – 48)                        | 35                   | 10.5 <sup>g</sup>                | (3.6 – 49)                        |  | VYSKOCIL et al. (1989)      |

**Tab. 9.1** Concentration of albumin in urine of solvent-exposed workers – results from cross-sectional and longitudinal studies

| Main compounds  | Concentration (mg/m <sup>3</sup> ) |           | Albumin (mg/g creatinine) |                                  |                     |                      |                                  |                    | Remarks   | Reference               |
|---|------------------------------------|-----------|---------------------------|----------------------------------|---------------------|----------------------|----------------------------------|--------------------|---|-------------------------|
|   |                                    |           | Exposed workers           |                                  |                     | Non-exposed controls |                                  |                    |   |                         |
|   | TWA                                | Range     | No.                       | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)  |   |                         |
| Styrene   | 100                                | 20-300    | 65                        | 6.4 <sup>g</sup><br>(GSD 2.2)    |                     | 59                   | 5.4 <sup>g</sup><br>(GSD 1.9)    |                    | VIAU et al.,<br>(1987b)                           |                         |
| C <sub>5</sub> – C <sub>7</sub> (cyclo)aliphatics, ethyl acetate, acetone | <sup>6</sup>                       |           | 182                       | 5.6<br>(SEM 0.2)                 |                     | 80                   | 5.9<br>(SEM 0.3)                 |                    | Hexanes concentration up to 800 mg/m <sup>3</sup> | MUTTI et al.<br>(1981)  |
| Aliphatic and aromatic hydrocarbons                                       |                                    | 1 – 156   | 53                        | <b>6.8<sup>g</sup></b>           | (2.76 – 54.9)       | 61                   | 4.8 <sup>g</sup>                 | (2.19 – 15.3)      |   | VIAU et al.<br>(1987)   |
| Naphtha blends  |                                    | 0.5 – 105 | 212                       |                                  | (33 positive tests) | 33                   |                                  | (0 positive tests) | Test-strip; sensitivity 0.15 – 0.3 g/l            | HASHIMOTO et al. (1991) |
| Naphtha blends  |                                    | 9 – 590   | 248                       | 10.2<br>(SD 26.4)                |                     | -                    | -                                | -                  | No control group                                  | ROCKSKAY et al. (1993)  |
| Naphtha blends  |                                    | 4 – 790   | 172                       | 6.9<br>(SD 28.5)                 |                     | -                    | -                                | -                  | No control group                                  | ROCKSKAY et al. (1993)  |
| Petroleum naphtha   | 1619                               |           | 48                        | 9.96 <sup>g</sup>                | (2.4 – 65.3)        | 23                   | 8 <sup>g</sup>                   | (1.9 – 36.1)       |   | VYSKOCIL et al. (1991)  |
| Not reported (refinery workers)   | not reported                       |           | 58                        | 5.2                              |                     | 65                   | 6.2                              |                    | < 10 a production work                            | GRUENER (1992)          |
|   |                                    |           | 18                        | 7.3                              |                     |                      |                                  |                    | > 10 a production work                            |                         |
|   |                                    |           | 42                        | 5.6                              |                     |                      |                                  |                    | Maintenance staff                                 |                         |

| Main compounds    | Concentration (mg/m <sup>3</sup> ) |                                     | Albumin (mg/g creatinine) |                                   |                         |                      |                                   |                    | Remarks  | Reference               |
|-------------------|------------------------------------|-------------------------------------|---------------------------|-----------------------------------|-------------------------|----------------------|-----------------------------------|--------------------|--|-------------------------|
|                   |                                    |                                     | Exposed workers           |                                   |                         | Non-exposed controls |                                   |                    |  |                         |
|                   | TWA                                | Range                               | No.                       | Mean <sup>a</sup><br>(SD or SEM)  | Median<br>(range)       | No.                  | Mean <sup>a</sup><br>(SD or SEM)  | Median<br>(range)  |  |                         |
| Ethylene glycol   |                                    | ≤ 22<br>(vapor)<br>76-190<br>(mist) | 33                        | 5.39 <sup>g</sup><br>(GSD 1.94)   |                         |                      | –                                 | –                  | End-of-shift values after day of aircraft de-icing, longitudinal study, no control group | GERIN et al. (1997)     |
|                   |                                    |                                     | 33                        | 4.20 <sup>g</sup><br>(GSD1.80)    |                         |                      | –                                 | –                  | End-of-shift values in period without de-icing, longitudinal study, no control group     |                         |
| Tetrachloroethene | 7.9                                | 1 – 221                             | 82                        |                                   | 3.8<br>(0.4 – 733)      | 19                   |                                   | 3.3<br>(0.7 – 9.3) |  | VERPLANKE et al. (1999) |
| Tetrachloroethene | ca. 70 <sup>2</sup>                |                                     | 57                        | ca. 5 <sup>g</sup>                |                         | 80                   | ca. 5 <sup>g</sup>                |                    | Values estimated from figures  | FRANCHINI et al. (1983) |
| Tetrachloroethene | 100 <sup>2</sup>                   | trace – 590                         | 50                        | 7.8 <sup>g</sup><br>(GSD 2.5)     |                         | 50                   | 5.2 <sup>g</sup><br>(GSD 1.7)     |                    | High values (>15.4) more frequent in exposed group                                       | MUTTI et al. (1992)     |
| Tetrachloroethene | 100 <sup>2</sup>                   | 0 – 950                             | 192                       | 40 <sup>5</sup><br>(SD 310)       | <10 – 4190 <sup>5</sup> | –                    | –                                 | –                  | Low participation; no control group  | SOLET and ROBINS (1991) |
| Tetrachloroethene | 145 <sup>2</sup>                   | 62 – 262                            | 26                        | 15 (8.1 <sup>g</sup> )<br>(SD 21) |                         | 33                   | 18 (7.2 <sup>g</sup> )<br>(SD 56) |                    |  | LAUWERYS et al. (1983)  |
| Tetrachloroethene | 157                                | 9 – 799                             | 16                        | 19.1 <sup>g</sup>                 | (7.7 – 97.2)            | 13                   | 18.9 <sup>g</sup>                 | (5.7 – 61.4)       |  | VYSKOCIL et al. (1990)  |

| Main compounds                                     | Concentration (mg/m <sup>3</sup> ) |             | Albumin (mg/g creatinine) |                                  |                     |                      |                                  |  | Remarks   | Reference                   |
|--|------------------------------------|-------------|---------------------------|----------------------------------|---------------------|----------------------|----------------------------------|--|---|-----------------------------|
|  |                                    |             | Exposed workers           |                                  |                     | Non-exposed controls |                                  |  |   |                             |
|  | TWA                                | Range       | No.                       | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)                        |   |                             |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP | < 3<br>< 1<br>< 2<br>< 0.25        |             | 73                        | <b>8.09</b>                      | 4.76<br>(0.2 – 178) | 35                   | 4.68                             | 3.62<br>(0.1 – 16)                       |   | BOOGAARD et al. (1993)      |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP |                                    |             | 93                        |                                  | 5.8<br>(2.0 – 117)  | 60<br>50             |                                  | 5.7<br>(2.5 – 215)<br>4.7<br>(2.1 – 113) | Controls with shift work (from petroleum refinery) controls without shift-work;<br>64 exposed also in BOOGAARD et al. (1993); albumin increase related to shift-work? | BOOGAARD and CAUBO (1994)   |
| 1,3-DCP  |                                    |             | 16                        | 2.55<br>(SD 1.66)                |                     |                      |                                  |  | Same workers, data after exposure-free weekend  | OSTERLOH and FELDMAN (1993) |
|  |                                    | 0.26 - 9.39 | 16                        | 3.06<br>(SD 1.66)                |                     |                      |                                  |  | Data after morning of one day with exposure   |                             |
|  |                                    | 0.26 - 9.39 | 15                        | 3.60<br>(SD 2.32)                |                     |                      |                                  |  | Data after afternoon of one day with exposure   |                             |
|  |                                    |             | 16                        | 1.99<br>(SD 1.26)                |                     |                      |                                  |  | Data on late evening of one day with exposure   |                             |

| Main compounds | Concentration (mg/m <sup>3</sup> ) |       | Albumin (mg/g creatinine) |                                  |                   |                      |                                  |                   | Remarks                                     | Reference                   |
|----------------|------------------------------------|-------|---------------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---|-----------------------------|
|                |                                    |       | Exposed workers           |                                  |                   | Non-exposed controls |                                  |                   |   |                             |
|                | TWA                                | Range | No.                       | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |                             |
| 1,3-DCP        |                                    |       | 16                        | 2.43<br>(SD 2.24)                |                   |                      |                                  |                   | Data next morning after one day of exposure | OSTERLOH and FELDMAN (1993) |

| Main compounds  | Concentration (mg/m <sup>3</sup> ) |                  | Albumin (mg/l)  |                                  |                     |                      |                                  |                     | Remarks   | Reference                |
|-----------------|------------------------------------|------------------|-----------------|----------------------------------|---------------------|----------------------|----------------------------------|---------------------|---|--------------------------|
|                 |                                    |                  | Exposed workers |                                  |                     | Non-exposed controls |                                  |                     |   |                          |
|                 | TWA                                | Range            | No.             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   |   |                          |
| Styrene         |                                    | 20 – 100         | 52              | <b>23.0</b><br>(SD 65.9)         | 4.9<br>(1 – 440)    | 48                   | 3.7<br>(SD 3.7)                  | 3.1<br>(0 – 21)     | Peak concentrations up to 925 mg/m <sup>3</sup>                 | ASKERGREN et al. (1981a) |
| Toluene         |                                    | 300 – 400        | 42              | 8.7<br>(SD 24.9)                 | 3.2<br>(0 – 163)    | 48                   | 3.7<br>(SD 3.7)                  |                     |   |                          |
| Xylene, toluene |                                    | see <sup>1</sup> | 39              | <b>13.7</b><br>(SD 32.2)         | 3.2<br>(0 – 130)    | 48                   | 3.7<br>(SD 3.7)                  |                     |   |                          |
| 1,3-DCP         | 1.9 – 18.9                         |                  | 14              |                                  | 7.6<br>(2.7 – 37.0) | 14                   |                                  | 5.2<br>(1.6 – 31.8) | Data from same group of workers after and before working season | BROUWER et al. (1991)    |

| Main compounds                      | Concentration (mg/m <sup>3</sup> ) |              | Albumin excretion (µg/min) |                                  |                     |                      |                                  |                     | Remarks   | Reference |
|-------------------------------------|------------------------------------|--------------|----------------------------|----------------------------------|---------------------|----------------------|----------------------------------|---------------------|---|-----------|
|                                     |                                    |              | Exposed workers            |                                  |                     | Non-exposed controls |                                  |                     |   |           |
|                                     | TWA                                | Range        | No.                        | Mean <sup>2</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>2</sup><br>(SD or SEM) | Median<br>(range)   |   |           |
| Toluene-containing solvent mixtures |                                    | <sup>4</sup> | 39                         | 6.38<br>(SEM 0.62)               |                     | 36                   | 7.63<br>(SEM 1.01)               |                     | KRUSELL et al. (1985)   |           |
| Toluene, xylene, styrene            |                                    |              |                            |                                  |                     | 48                   | 1.7<br>(SD 1.6)                  |                     | Values given for control group only<br>ASKERGREN et al. (1981a)   |           |
| Toluene, methanol                   |                                    |              | 245                        | 5.8                              | 5.3<br>(0.1 – 1335) | 67                   | 5.2                              | 4.6<br>(0.3 – 39.8) | Exposure scores, not related to lifetime exposure, present occupation or exposure duration, effects more pronounced in subgroup with hypertension<br>HOTZ et al. (1990) |           |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: TWA varied between 10 and 50 % of Swedish hygiene limit for toluene (300 mg/m<sup>3</sup>) and xylene (350 mg/m<sup>3</sup>)

2: values given in ppm in original reference

3: 1,3-dichloropropene: roughly equal mixture of Z/E-isomers

4: reported exposure level on average 0.5 x threshold limit values

5: In the original reference, values are given as unitless "albumin/creatinine ratios" which most likely correspond to g albumin/g creatinine

6: sum of hexanes at most workplaces exceeded TLV

7: values given as mg albumin/mmol creatinine in original reference; (MG creatinine: 113,12 g/mol)

**Tab. 9.2** Concentration of  $\beta_2$ -microglobulin ( $\beta_2$ M) in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds                      | Concentration (mg/m <sup>3</sup> ) |                                     | $\beta_2$ M ( $\mu$ g/g creatinine) |                                  |                   |                      |                                  |                   | Remarks   | Reference           |
|-------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---|---------------------|
|                                     |                                    |                                     | Exposed workers                     |                                  |                   | Non-exposed controls |                                  |                   |   |                     |
|                                     | TWA                                | Range                               | No.                                 | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |                     |
| Toluene                             | 141                                |                                     | 92                                  | 50.4 <sup>g</sup><br>(GSD 16.8)  |                   | 74                   | 60.1 <sup>g</sup><br>(GSD 15.9)  |                   | STENGEL et al. (1998)   |                     |
| Styrene                             | 225                                | 83 – 366                            | 37                                  | 45.3 <sup>g</sup>                | (13 – 97)         | 35                   | 54.7 <sup>g</sup>                | (13.4 – 132)      | VYSKOCIL et al. (1989)  |                     |
| Styrene                             | 100                                | 20-300                              | 65                                  | 63 <sup>g</sup><br>(GSD 21.7)    |                   | 59                   | 53 <sup>g</sup><br>(GSD 2.0)     |                   | VIAU et al. (1987b)   |                     |
| Aliphatic and aromatic hydrocarbons |                                    | 1 – 156                             | 53                                  | 77 <sup>g</sup>                  | (36 – 632)        | 61                   | 68 <sup>g</sup>                  | (26 – 550)        | VIAU et al. (1987)  |                     |
| Naphtha blends                      |                                    | 4 – 790                             | 168                                 | 450<br>(SD 330)                  |                   | -                    | -                                | -                 | No control group<br>ROCSKAY et al. (1993)                                 |                     |
| Petroleum naphtha                   | 1619                               |                                     | 48                                  | 46.6 <sup>g</sup>                | (11.5 – 235.3)    | 23                   | 33.3 <sup>g</sup>                | (4.6 – 231)       | VYSKOCIL et al. (1991)  |                     |
| Ethylene glycol                     |                                    | ≤ 22<br>(vapor)<br>76-190<br>(mist) | 33                                  | 43.19 <sup>g</sup><br>(GSD 1.94) |                   |                      | -                                | -                 | End-of-shift values after day of aircraft de-icing , no control group     | GERIN et al. (1997) |
|                                     |                                    |                                     | 33                                  | 44.26 <sup>g</sup><br>(GSD 3.01) |                   |                      | -                                | -                 | End-of-shift values in period without de-icing, no control group          |                     |
| Tetrachloro-ethene                  | 100 <sup>2</sup>                   | trace – 590                         | 50                                  | 43.6 <sup>g</sup><br>(GSD 2.5)   |                   | 50                   | 34.6 <sup>g</sup><br>(GSD 2.4)   |                   | High values (>97.8) more frequent in exposed group<br>MUTTI et al. (1992) |                     |



| Main compounds                                     | Concentration (mg/m <sup>3</sup> ) |          | β <sub>2</sub> M (μg/g creatinine) |                                  |                   |                      |                                  |  | Remarks   | Reference                 |
|--|------------------------------------|----------|------------------------------------|----------------------------------|-------------------|----------------------|----------------------------------|--|---|---------------------------|
|  |                                    |          | Exposed workers                    |                                  |                   | Non-exposed controls |                                  |  |   |                           |
|  | TWA                                | Range    | No.                                | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)                        |   |                           |
| Tetrachloroethene                                  | 145 <sup>2</sup>                   | 62 – 262 | 26                                 | 63<br>(SD 67)                    |                   | 33                   | 81<br>(SD 83)                    |  | LAUWERYS et al. (1983)  |                           |
| Tetrachloroethene                                  | 157                                | 9 – 799  | 16                                 | 63.9 <sup>g</sup>                | (9.9 – 333.3)     | 13                   | 45.0 <sup>g</sup>                | (11.7 – 153.6)                           | VYSKOCIL et al. (1990)  |                           |
| Trichloroethene                                    | 80 <sup>2</sup>                    |          | 104                                | 129.0<br>(SD 113.3)              |                   | 102                  | 113.6<br>(SD 110.6)              |  | NAGAYA et al. (1989)  |                           |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP |                                    |          | 93                                 |                                  | 59<br>(13 – 375)  | 60<br>50             |                                  | 57.5<br>(14 – 306)<br>64.5<br>(15 – 446) | Controls with shift work<br><br>Controls without shift-work,<br>64 exposed workers also in BOOGAARD et al. (1993) | BOOGAARD and CAUBO (1994) |

| Main compounds  | Concentration (mg/m <sup>3</sup> ) |                  | β <sub>2</sub> M (μg/l) |                                  |                         |                      |                                  |                        | Remarks   | Reference                |
|-----------------|------------------------------------|------------------|-------------------------|----------------------------------|-------------------------|----------------------|----------------------------------|------------------------|---|--------------------------|
|                 |                                    |                  | Exposed workers         |                                  |                         | Non-exposed controls |                                  |                        |   |                          |
|                 | TWA                                | Range            | No.                     | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)       | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)      |   |                          |
| Styrene         |                                    | 20 – 100         | 52                      | 191<br>(SD 187)                  | 140                     | 48                   | 259<br>(SD 393)                  | 134<br>(0 – 1840)      | Peak concentrations up to 925 mg/m <sup>3</sup>   | ASKERGREN et al. (1981a) |
| Toluene         |                                    | 300 – 400        | 42                      | 112<br>(SD 75)                   | 97                      | 48                   | 259<br>(SD 393)                  | 134<br>(0 – 1840)      |   |                          |
| Xylene, toluene |                                    | see <sup>1</sup> | 40                      | 255<br>(656)                     | 99                      | 48                   | 259<br>(SD 393)                  | 134<br>(0 – 1840)      |   |                          |
| 1,3-DCP         | 1.9 – 18.9                         |                  | 12                      |                                  | 109.9<br>(65.3 – 350.9) | 8                    |                                  | 76.4<br>(45.0 – 174.3) | Data from same group of workers before and after working season, 8 out of 28 urine samples excluded because of pH < 5.5 | BROUWER et al. (1991)    |

| Main compounds                      | Concentration (mg/m <sup>3</sup> ) |       | $\beta_2$ M excretion ( $\mu$ g/min) |                                  |                   |                      |                                  |                   | Remarks               | Reference |
|-------------------------------------|------------------------------------|-------|--------------------------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|-----------------------|-----------|
|                                     |                                    |       | Exposed workers                      |                                  |                   | Non-exposed controls |                                  |                   |                       |           |
|                                     | TWA                                | Range | No.                                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |                       |           |
| Toluene containing solvent mixtures |                                    | 4     | 39                                   | 0.086<br>(SEM 0.007)             |                   | 36                   | 0.088<br>(SEM 0.011)             |                   | KRUSELL et al. (1985) |           |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: TWA varied between 10 and 50 % of Swedish hygiene limit for toluene (300 mg/m<sup>3</sup>) and xylene (350 mg/m<sup>3</sup>)

2: values given in ppm in original reference.

3: 1,3-dichloropropene: roughly equal mixture of Z/E-isomers

4: reported exposure level on average 0.5 x threshold limit values

5: In the original reference, values are given as unitless "albumin/creatinine ratios" which most likely correspond to g albumin/g creatinine

6: sum of hexanes at most workplaces exceeded TLV

7: values given as mg albumin/mmol creatinine in original reference; (MG creatinine: 113,12 g/mol)

**Tab. 9.3** Concentration of retinol-binding protein (RBP) in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds   | Concentration (mg/m <sup>3</sup> ) | RBP ( $\mu\text{g/g creatinine}$ )       |       |                                  |                                  |                      |                               |                                  | Remarks   | Reference                   |
|------------------|------------------------------------|--|-------|----------------------------------|----------------------------------|----------------------|-------------------------------|----------------------------------|---|-----------------------------|
|                  |                                    | Exposed workers                          |       |                                  |                                  | Non-exposed controls |                               |                                  |   |                             |
|                  |                                    | TWA                                      | Range | No.                              | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    | No.                           | Mean <sup>a</sup><br>(SD or SEM) |   |                             |
| Styrene          | 113                                |  | 5     | 69.2 <sup>g</sup>                |                                  | 5                    | 40.89 <sup>g</sup>            |                                  | Overnight urine samples   | VERPLANKE and HERBER (1998) |
|                  |                                    |  | 5     | 33.14 <sup>g</sup>               |                                  | 5                    | 35.58 <sup>g</sup>            |                                  | End-of-shift-sample   |                             |
| Styrene          | 225                                | 83 – 366                                 | 37    | 156 <sup>g</sup>                 | (71 – 633)                       | 35                   | 175 <sup>g</sup>              | (52 – 385)                       |   | VYSKOCIL et al. (1989)      |
| Styrene          | 100                                | 20 – 300                                 | 65    | 108 <sup>g</sup><br>(GSD 1.6)    |                                  | 59                   | 105 <sup>g</sup><br>(GSD 1.7) |                                  |   | VIAU et al. (1987b)         |
| Toluene          | < 380 <sup>2</sup>                 |  | 45    |                                  | 159<br>(18 – 2274)               | 45                   |                               | 88<br>(26 – 557)                 | ↑ prevalence of elevated values ( $\geq 265 \mu\text{g/g}$ )          | NG et al. (1990)            |
| 2-butoxy-ethanol | 2.91                               |  | 31    | 96.8<br>(SD 37.4)                | (39.0 – 178.3)                   | 21                   | 128.8<br>(SD 167.3)           | (26 – 827.5)                     |   | HAUFROID et al. (1997)      |
| Ethylene glycol  |                                    | $\leq 22$<br>(vapor)<br>76-190<br>(mist) | 33    | 51.16<br>(GSD 1.62)              |                                  |                      | –                             | –                                | End-of-shift values after day of aircraft de-icing , no control group | GERIN et al. (1997)         |
|                  |                                    |  | 33    | 50.47 <sup>g</sup><br>(GSD 1.66) |                                  |                      | –                             | –                                | End-of-shift values in period without de-icing , no control group     |                             |

| Main compounds  | Concentration (mg/m <sup>3</sup> ) | RBP ( $\mu\text{g/g creatinine}$ ) |       |                                |                                  |                      |                                |                                  | Remarks   | Reference                   |
|---|------------------------------------|------------------------------------|-------|--------------------------------|----------------------------------|----------------------|--------------------------------|----------------------------------|---|-----------------------------|
|   |                                    | Exposed workers                    |       |                                |                                  | Non-exposed controls |                                |                                  |   |                             |
|   |                                    | TWA                                | Range | No.                            | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    | No.                            | Mean <sup>a</sup><br>(SD or SEM) |   |                             |
| Aliphatic and aromatic hydrocarbons                             |                                    | 1 – 156                            | 53    | 79 <sup>g</sup>                | (31.3 – 275)                     | 61                   | 82 <sup>g</sup>                | (22 – 178)                       |   | VIAU et al. (1987)          |
| Petroleum naphtha   | 1619                               |                                    | 48    | 50 <sup>g</sup>                | (12 – 250)                       | 23                   | 81 <sup>g</sup>                | (20 – 1300)                      |   | VYSKOCIL et al. (1991)      |
| Tetrachloro-ethene  | 7.9                                | 1 – 221                            | 82    | <b>75.4<sup>g</sup></b>        |                                  | 19                   | 41.6 <sup>g</sup>              |                                  |   | VERPLANKE et al. (1999)     |
| Tetrachloro-ethene  | 100 <sup>2</sup>                   | trace – 590                        | 50    | 54.7 <sup>g</sup><br>(GSD 1.6) |                                  | 50                   | 50.1 <sup>g</sup><br>(GSD 1.6) |                                  | High values ( $\geq 90$ ) more often in exposed group | MUTTI et al. (1992)         |
| Tetrachloro-ethene  | 145 <sup>2</sup>                   | 62 – 262                           | 26    | 60<br>(SD 42)                  |                                  | 33                   | 50<br>(SD 38)                  |                                  |   | LAUWERYS et al. (1983)      |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP <sup>3</sup> | < 3<br>< 1<br>< 2<br>< 0.25        |                                    | 73    | 75.8                           | 65.7<br>(5 – 361)                | 35                   | 76.3                           | 63.9<br>(4 – 233)                |   | BOOGAARD et al. (1993)      |
| 1,3-DCP   |                                    |                                    | 16    | 25.05<br>(SD 19.31)            |                                  |                      |                                |                                  | Same workers, data after exposure-free weekend        | OSTERLOH and FELDMAN (1993) |
|   |                                    | 0.26 - 9.39                        | 16    | 31.86<br>(SD 25.74)            |                                  |                      |                                |                                  | Data after morning of one day with exposure           |                             |

| Main compounds | Concentration (mg/m <sup>3</sup> ) | RBP ( $\mu\text{g/g creatinine}$ ) |       |                     |                                  |                      |     |                                  | Remarks                                       | Reference                   |
|----------------|------------------------------------|------------------------------------|-------|---------------------|----------------------------------|----------------------|-----|----------------------------------|---|-----------------------------|
|                |                                    | Exposed workers                    |       |                     |                                  | Non-exposed controls |     |                                  |   |                             |
|                |                                    | TWA                                | Range | No.                 | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    | No. | Mean <sup>a</sup><br>(SD or SEM) |   |                             |
| 1,3-DCP        |                                    | 0.26 - 9.39                        | 15    | 16.85<br>(SD 10.64) |                                  |                      |     |                                  | Data after afternoon of one day with exposure | OSTERLOH and FELDMAN (1993) |
|                |                                    |                                    | 16    | 17.97<br>(SD 14.00) |                                  |                      |     |                                  | Data on late evening of one day with exposure |                             |
|                |                                    |                                    | 16    | 30.88<br>(SD 35.15) |                                  |                      |     |                                  | Data next morning after one day of exposure   |                             |

| Main compounds | Concentration (mg/m <sup>3</sup> ) | RBP (µg/l)      |       |     |                                  |                      |     |                                  | Remarks   | Reference             |
|----------------|------------------------------------|-----------------|-------|-----|----------------------------------|----------------------|-----|----------------------------------|---|-----------------------|
|                |                                    | Exposed workers |       |     |                                  | Non-exposed controls |     |                                  |   |                       |
|                |                                    | TWA             | Range | No. | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    | No. | Mean <sup>a</sup><br>(SD or SEM) |   |                       |
| 1,3-DCP        | 1.9 – 18.9                         |                 | 14    |     | <b>26.9</b><br>(16.5 – 72.7)     | 14                   |     | 20.0<br>(8.4 – 36.1)             | Data from same group of workers before and after working season | BROUWER et al. (1991) |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: TWA varied between 10 and 50 % of Swedish hygiene limit for toluene (300 mg/m<sup>3</sup>) and xylene (350 mg/m<sup>3</sup>)

2: values given in ppm in original reference

3: 1,3-dichloropropene: roughly equal mixture of Z/E-isomers

4: reported exposure level on average 0.5 x threshold limit values

5: In the original reference, values are given as unitless "albumin/creatinine ratios" which most likely correspond to g albumin/g creatinine;

6: sum of hexanes at most workplaces exceeded TLV

7: values given as mg albumin/mmol creatinine in original reference; (MG creatinine: 113,12 g/mol).

| Main compounds                      | Concentration (mg/m <sup>3</sup> ) |          | NAG (U/g creatinine) |                                  |                   |                      |                                  |                   | Remarks   | Reference |
|-------------------------------------|------------------------------------|----------|----------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---|-----------|
|                                     |                                    |          | Exposed workers      |                                  |                   | Non-exposed controls |                                  |                   |   |           |
|                                     | TWA                                | Range    | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |           |
| Toluene                             | 141                                |          | 92                   | 2.0 <sup>g</sup><br>(GSD 14.5)   |                   | 74                   | 1.9 <sup>g</sup><br>(GSD 14.5)   |                   | STENGEL et al. (1998)                               |           |
| Styrene                             | 113                                |          | 5                    | 1.06 <sup>g</sup>                |                   | 5                    | 1.57 <sup>g</sup>                |                   | Overnight urine samples                             |           |
|                                     |                                    |          | 5                    | 2.38 <sup>g</sup>                |                   | 5                    | 2.46 <sup>g</sup>                |                   | End-of-shift-samples                                |           |
| Styrene                             | 225                                | 83 – 366 | 37                   | 1.69<br>(SEM 0.11)               |                   | 35                   | 1.67<br>(SEM 0.13)               |                   | Average of first/last workday pre-/postshift values |           |
|                                     |                                    |          | 37                   | <b>1.73</b><br>(SEM 0.13)        |                   | 35                   | 1.38<br>(SEM 0.11)               |                   | End of last workday values                          |           |
| Aliphatic and aromatic hydrocarbons |                                    | 1 – 156  | 53                   | 1.24 <sup>g</sup>                | (0.19 – 4.42)     | 61                   | 1.16 <sup>g</sup>                | (0.33 – 5.21)     | VIAU et al. (1987)                                  |           |
| Naphtha blends                      |                                    | 9 – 590  | 248                  | 1.30<br>(SD 1.20)                |                   | -                    | -                                | -                 | No control group                                    |           |
| Naphtha blends                      |                                    | 4 – 790  | 180                  | 1.90<br>(SD 1.20)                |                   | -                    | -                                | -                 | No control group                                    |           |
| Petroleum naphtha                   | 1619                               |          | 48                   | <b>3.55<sup>g</sup></b>          | (0.3 – 21.9)      | 23                   | 1.61 <sup>g</sup>                | (0.2 – 6.4)       | High values more frequent in exposed group          |           |

**Tab. 9.4** N-acetyl-β-D-glucosaminidase (NAG) activity in urine of solvent-exposed workers – results from cross-sectional studies



| Main compounds                                  | Concentration (mg/m <sup>3</sup> ) |       | NAG (U/g creatinine) |                                  |                             |                      |                                  |                             | Remarks   | Reference                      |
|---|------------------------------------|-------|----------------------|----------------------------------|-----------------------------|----------------------|----------------------------------|-----------------------------|---|--------------------------------|
|   |                                    |       | Exposed workers      |                                  |                             | Non-exposed controls |                                  |                             |   |                                |
|   | TWA                                | Range | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)           | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)           |   |                                |
| Paint solvents<br>(used by painters)            |                                    |       | 73                   |                                  | 2.7<br>(0.7 – 21.4)         | 102                  |                                  | 3.7<br>(0.9 – 16.7)         | No measured solvent concentrations reported; NAG sign. ↓ than in controls   | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers)            |                                    |       | 104                  |                                  | 4.6<br>(1.0 – 24.3)         | 102                  |                                  | 3.7<br>(0.9 – 16.7)         | No measured solvent concentrations reported   | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers)            |                                    |       | 112                  |                                  | (ca. 1.3 – 16) <sup>7</sup> | 92                   |                                  | (ca. 0.9 – 13) <sup>7</sup> | No measured solvent concentrations reported; NAG-activity estimated from figures; high values more frequent in exposed groups | YAQOOB et al. (1993)           |
| Petroleum-based mineral oils                    |                                    |       | 101                  |                                  | (ca. 0.9 – 19) <sup>7</sup> | 92                   |                                  | (ca. 0.9 – 13) <sup>7</sup> |   |                                |
| Not reported<br>(refinery workers)              | not reported                       |       | 58                   | 6.5                              |                             | 65                   | 11.0                             |                             | < 10 a production work  | GRUENER (1992)                 |
|   |                                    |       | 18                   | 10.0                             |                             |                      |                                  |                             | > 10 a production work  |                                |
|   |                                    |       | 42                   | 5.0                              |                             |                      |                                  |                             | Maintenance staff   |                                |
| Trichloroethene<br>freon 113<br>trichloroethane |                                    |       | 82                   | 0.89<br>(SD 0.62) <sup>8</sup>   |                             | 48                   | 0.62<br>(SD 0.40) <sup>8</sup>   |                             | No correlation with TCA-excretion; positive control: diabetics with/without nephropathy                                       | BROGREN et al. (1986)          |

| Main compounds  | Concentration (mg/m <sup>3</sup> ) |         | NAG (U/g creatinine) |                                  |                     |                      |                                  |                     | Remarks  | Reference               |
|---|------------------------------------|---------|----------------------|----------------------------------|---------------------|----------------------|----------------------------------|---------------------|--|-------------------------|
|   |                                    |         | Exposed workers      |                                  |                     | Non-exposed controls |                                  |                     |  |                         |
|   | TWA                                | Range   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   |  |                         |
| Trichloroethene, freon 113                                      | not reported                       |         | 85                   | 0.89<br>(SEM 0.065)              | (0.19 – 3.23)       |                      |                                  |                     | No external control group; values in original reference reported as µmol 4-methylumbelliferone released/ (h · g creatinine)                                | RASMUSSEN et al. (1993) |
| Trichloroethene   | 27                                 |         | 29                   | 1.50<br>(SD 0.97)                |                     |                      | 1.68<br>(SD 0.97)                |                     | Controls: reference values from analytical laboratory:<br>values in original reference reported as µmol 4-methylumbelliferone released/ (h · g creatinine) | SELDEN et al. (1993)    |
| Tetrachloroethene   | 7.9                                | 1 – 221 | 82                   | 1.52                             |                     | 19                   | 1.64                             |                     |  | VERPLANKE et al. (1999) |
| Tetrachloroethene   | 100 <sup>2</sup>                   | 0 – 950 | 192                  | 2.19<br>(SD 1.99)                | 0.46 – 19.18        |                      |                                  |                     | Low participation; no control group  | SOLET and ROBINS (1991) |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP <sup>3</sup> | < 3<br>< 1<br>< 2<br>< 0.25        |         | 73                   | 1.37                             | 1.15<br>(0.3 – 5.5) | 35                   | 1.42                             | 1.06<br>(0.1 – 4.2) |  | BOOGAARD et al. (1993)  |

| Main compounds                                     | Concentration (mg/m <sup>3</sup> ) |                | NAG (U/g creatinine) |                                  |                     |                      |                                  |                     | Remarks  | Reference                            |
|--|------------------------------------|----------------|----------------------|----------------------------------|---------------------|----------------------|----------------------------------|---------------------|--|--------------------------------------|
|  |                                    |                | Exposed workers      |                                  |                     | Non-exposed controls |                                  |                     |  |                                      |
|  | TWA                                | Range          | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   |  |                                      |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP |                                    |                | 93                   |                                  | 1.03<br>(0.1 – 3.7) | 60                   |                                  | 1.18<br>(0.3 – 2.7) | Controls with shift work<br>(oil refinery workers)<br>control without shift-<br>work;<br>64 exposed workers<br>also in BOOGAARD et<br>al. (1993) | BOOGAARD<br>and CAUBO<br>(1994)      |
|  |                                    |                |                      |                                  |                     | 50                   |                                  | 1.24<br>(0.2 – 3.1) |  |                                      |
| 1,3-DCP  |                                    |                | 16                   | 2.45<br>(SD 1.06)                |                     |                      |                                  |                     | Same workers, data<br>after exposure-free<br>weekend   | OSTERLOH<br>and<br>FELDMAN<br>(1993) |
|  |                                    | 0.26 -<br>9.39 | 16                   | 2.85<br>(SD 1.62)                |                     |                      |                                  |                     | Data after morning of<br>one day with exposure   |                                      |
|  |                                    | 0.26 -<br>9.39 | 15                   | 2.44<br>(SD 0.91)                |                     |                      |                                  |                     | Data after afternoon of<br>one day with exposure   |                                      |
|  |                                    |                | 16                   | 2.72<br>(SD 1.05)                |                     |                      |                                  |                     | Data on late evening of<br>one day with exposure   |                                      |
|  |                                    |                | 16                   | 2.79<br>(SD 1.40)                |                     |                      |                                  |                     | data next morning after<br>one day of exposure   |                                      |

| Main compounds     | Concentration (mg/m <sup>3</sup> ) |             | NAG (U/ml GFR)  |                                  |                   |                      |                                  |                   | Remarks             | Reference |
|--------------------|------------------------------------|-------------|-----------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---------------------|-----------|
|                    |                                    |             | Exposed workers |                                  |                   | Non-exposed controls |                                  |                   |                     |           |
|                    | TWA                                | Range       | No.             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |                     |           |
| Tetrachloro-ethene | 100 <sup>2</sup>                   | trace – 590 | 50              | 0.104 <sup>g</sup><br>(GSD 2.9)  |                   | 50                   | 0.113 <sup>g</sup><br>(GSD 2.4)  |                   | MUTTI et al. (1992) |           |

| Main compounds                       | Concentration (mg/m <sup>3</sup> ) |       | NAG (U/l)       |                                  |                     |                      |                                  |                     | Remarks   | Reference                      |
|--------------------------------------|------------------------------------|-------|-----------------|----------------------------------|---------------------|----------------------|----------------------------------|---------------------|---|--------------------------------|
|                                      |                                    |       | Exposed workers |                                  |                     | Non-exposed controls |                                  |                     |   |                                |
|                                      | TWA                                | Range | No.             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)   |   |                                |
| Paint solvents<br>(used by painters) |                                    |       | 74              |                                  | 2.5<br>(1.0 – 15.0) | 102                  |                                  | 4.1<br>(0.8 – 26.0) | No measured solvent concentrations reported; NAG sign. ↓ than in controls | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers) |                                    |       | 104             |                                  | 6.0<br>(1.2 – 39.0) | 102                  |                                  | 4.1<br>(0.8 – 26.0) | No measured solvent concentrations reported                               |                                |

a: arithmetic mean, if not otherwise indicated; g: geometric mean; GSD: geometric standard deviation

1: TWA varied between 10 and 50 % of Swedish hygiene limit for toluene (300 mg/m<sup>3</sup>) and xylene (350 mg/m<sup>3</sup>)

2: values given in ppm in original reference

3: 1,3-dichloropropene: roughly equal mixture of Z/E-isomers

4: reported exposure level on average 0.5 x threshold limit values

5: In the original reference, values are given as unitless "albumin/creatinine ratios" which most likely correspond to g albumin/g creatinine

6: sum of hexanes at most workplaces exceeded TLV

7: values given as mg albumin/mmol creatinine in original reference; (MG creatinine: 113,12 g/mol)

8: values given as µmol 4-methylumbelliferon/(h g creatinine) in original reference

**Tab. 9.5**  $\beta$ -galactosidase ( $\beta$ Gal) activity in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds    | Concentration (mg/m <sup>3</sup> ) |         | $\beta$ -Galactosidase (U/g creatinine) |                                  |                   |                      |                                  |                   | Remarks                 | Reference                   |
|-------------------|------------------------------------|---------|---|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|-------------------------|-----------------------------|
|                   |                                    |         | Exposed workers                         |                                  |                   | Non-exposed controls |                                  |                   |                         |                             |
|                   | TWA                                | Range   | No.                                     | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |                         |                             |
| Styrene           | 113                                |         | 5                                       | 1.89 <sup>g</sup>                |                   | 5                    | 1.44 <sup>g</sup>                |                   | Overnight urine samples | VERPLANKE and HERBER (1998) |
|                   |                                    |         | 5                                       | 1.18 <sup>g</sup>                |                   | 5                    | 1.20 <sup>g</sup>                |                   | End-of-shift-samples    |                             |
| Tetrachloroethene | 7.9                                | 1 – 221 | 82                                      | 2.12                             |                   | 19                   | 2.32                             |                   |                         | VERPLANKE et al. (1999)     |

| Main compounds | Concentration (mg/m <sup>3</sup> ) |       | $\beta$ -Galactosidase (U/l) |                                  |                    |                      |                                  |                    | Remarks   | Reference             |
|----------------|------------------------------------|-------|------------------------------|----------------------------------|--------------------|----------------------|----------------------------------|--------------------|---|-----------------------|
|                |                                    |       | Exposed workers              |                                  |                    | Non-exposed controls |                                  |                    |   |                       |
|                | TWA                                | Range | No.                          | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)  | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)  |   |                       |
| 1,3-DCP        | 1.9 – 18.9                         |       | 12                           |                                  | 2.4<br>(1.7 – 5.6) | 11                   |                                  | 1.9<br>(1.1 – 7.2) | Data from same group of workers before and after working season | BROUWER et al. (1991) |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

| Main compounds  | Concentration (mg/m <sup>3</sup> ) |         | AAP (U/g creatinine) |                                  |                      |                      |                                  |                      | Remarks                                     | Reference                      |
|---|------------------------------------|---------|----------------------|----------------------------------|----------------------|----------------------|----------------------------------|----------------------|---|--------------------------------|
|   |                                    |         | Exposed workers      |                                  |                      | Non-exposed controls |                                  |                      |   |                                |
|   | TWA                                | Range   | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    |   |                                |
| Toluene   | 141                                |         | 92                   | 5.2 <sup>g</sup><br>(GSD 13.2)   |                      | 74                   | 5.3 <sup>g</sup><br>(GSD 13.3)   |                      | STENGEL et al. (1998)                       |                                |
| Styrene   | 113                                |         | 5                    | 3.60 <sup>g</sup>                |                      | 5                    | 3.04 <sup>g</sup>                |                      | Overnight urine samples                     | VERPLANKE and HERBER (1998)    |
|   |                                    |         | 5                    | 4.49 <sup>g</sup>                |                      | 5                    | 3.35 <sup>g</sup>                |                      | End-of-shift-samples                        |                                |
| Paint solvents<br>(used by painters)                            |                                    |         | 63                   |                                  | 10.7<br>(0.6 – 55.7) | 102                  |                                  | 7.1<br>(1.3 – 104.6) | No measured solvent concentrations reported | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers)                            |                                    |         | 100                  |                                  | 6.3<br>(1.7 – 37.1)  | 102                  |                                  | 7.1<br>(1.3 – 104.6) | No measured solvent concentrations reported |                                |
| Tetrachloroethene   | 7.9                                | 1 – 221 | 82                   | 7.47                             |                      | 19                   | 7.23                             |                      |   | VERPLANKE et al. (1999)        |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP <sup>3</sup> | < 3<br>< 1<br>< 2<br>< 0.25        |         | 73                   | 2.78                             | 2.38<br>(1.1 – 9.4)  | 35                   | 2.85                             | 2.38<br>(1.1 – 8.2)  |   | BOOGAARD et al. (1993)         |

**Tab. 9.6** Alanine aminopeptidase (AAP) activity in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds                       | Concentration (mg/m <sup>3</sup> ) |       | AAP (U/I)       |                                  |                      |                      |                                  |                        | Remarks   | Reference                      |
|--------------------------------------|------------------------------------|-------|-----------------|----------------------------------|----------------------|----------------------|----------------------------------|------------------------|---|--------------------------------|
|                                      |                                    |       | Exposed workers |                                  |                      | Non-exposed controls |                                  |                        |   |                                |
|                                      | TWA                                | Range | No.             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)    | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)      |   |                                |
| Paint solvents<br>(used by painters) |                                    |       | 64              |                                  | 12.4<br>(1.0 – 56.0) | 102                  |                                  | 9.2<br>(0.5 – 157.0)   | No measured solvent concentrations reported                     | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers) |                                    |       | 100             |                                  | 7.9<br>(1.8 – 60.0)  | 102                  |                                  | 46.4<br>(12.0 – 502.0) | No measured solvent concentrations reported                     |                                |
| 1,3-DCP                              | 1.9 – 18.9                         |       | 13              |                                  | 8.3<br>(5.0 – 18.6)  | 12                   |                                  | 9.7<br>(6.5 – 13.9)    | Data from same group of workers before and after working season | BROUWER et al. (1991)          |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: TWA varied between 10 and 50 % of Swedish hygiene limit for toluene (300 mg/m<sup>3</sup>) and xylene (350 mg/m<sup>3</sup>)

2: values given in ppm in original reference

3: 1,3-dichloropropene: roughly equal mixture of Z/E-isomers

4: reported exposure level on average 0.5 x threshold limit values

5: In the original reference, values are given as unitless "albumin/creatinine ratios" which most likely correspond to g albumin/g creatinine

6: sum of hexanes at most workplaces exceeded TLV

7: values given as mg albumin/mmol creatinine in original reference; (MG creatinine: 113,12 g/mol).

| Main compounds   | Concentration (mg/m <sup>3</sup> ) |          | Total protein (mg/g creatinine) |                                  |                   |                      |                                  |                   | Remarks   | Reference               |
|--|------------------------------------|----------|---------------------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---|-------------------------|
|  |                                    |          | Exposed workers                 |                                  |                   | Non-exposed controls |                                  |                   |   |                         |
|  | TWA                                | Range    | No.                             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |                         |
| Toluene, xylene  | ca. 95<br>(toluene) <sup>2</sup>   |          | 118                             | ca. 49 <sup>g</sup>              |                   | 80                   | ca. 42 – 46                      |                   | Values estimated from figures, two control groups | FRANCHINI et al. (1983) |
| Styrene  | ca. 215 <sup>2</sup>               |          | 51                              | ca. 54 <sup>g</sup>              |                   | 80                   | ca. 42 – 46                      |                   | Values estimated from figures, two control groups | FRANCHINI et al. (1983) |
| Styrene  | 225                                | 83 – 366 | 37                              | 97.6<br>(SEM 12.6)               |                   | 35                   | 82.8<br>(SEM 13.1)               |                   |   | VYSKOCIL et al. (1989)  |
| C <sub>5</sub> – C <sub>7</sub> aliphatics/cycloaliphatics, ethyl acetate, acetone | <sup>6</sup>                       |          | 182                             | <b>60.3</b><br>(SEM 1.6)         |                   | 80                   | 48.3<br>(SEM 3.1)                |                   | Hexanes concentration up to 800 mg/m <sup>3</sup> | MUTTI et al. (1981)     |
| Naphtha blends   |                                    | 9 – 590  | 248                             | 40.6<br>(SD 51.0)                |                   | -                    | -                                | -                 | No control group                                  | ROCSKAY et al. (1993)   |
| Naphtha blends   |                                    | 4 – 790  | 180                             | 45.2<br>(SD 115.9)               |                   | -                    | -                                | -                 | No control group                                  | ROCSKAY et al. (1993)   |
| Petroleum naphtha  | 1619                               |          | 48                              | 121 <sup>g</sup>                 | (25 – 310)        | 23                   | 96 <sup>g</sup>                  | (25 – 270)        |   | VYSKOCIL et al. (1991)  |

**Tab. 9.7** Concentration of total protein (TP) in urine of solvent-exposed workers – results from cross-sectional studies



| Main compounds                       | Concentration (mg/m <sup>3</sup> ) |             | Total protein (mg/g creatinine) |                                  |                              |                      |                                  |                             | Remarks   | Reference                      |
|--------------------------------------|------------------------------------|-------------|---------------------------------|----------------------------------|------------------------------|----------------------|----------------------------------|-----------------------------|---|--------------------------------|
|                                      |                                    |             | Exposed workers                 |                                  |                              | Non-exposed controls |                                  |                             |   |                                |
|                                      | TWA                                | Range       | No.                             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)            | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)           |   |                                |
| Paint solvents<br>(used by painters) |                                    |             | 78                              |                                  | <b>41.4</b><br>(0.0 – 3260)  | 104                  |                                  | 46.4<br>(12.0 – 502)        | No measured solvent concentrations reported; TP sign. ↓ than in controls  | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers) |                                    |             | 104                             |                                  | <b>62.7</b><br>(3.0 – 254.0) | 104                  |                                  | 46.4<br>(12.0 – 502)        | No measured solvent concentrations reported   |                                |
| Paint solvents<br>(used by sprayers) |                                    |             | 112                             |                                  | (ca. 18 - 177) <sup>7</sup>  | 92                   |                                  | (ca. 31 - 186) <sup>7</sup> | No measured solvent concentrations reported; protein values estimated from figures, high values more frequent in exposed groups | YAQOOB et al. (1993)           |
| Petroleum-based mineral oils         |                                    |             | 101                             |                                  | (ca. 31 - 186) <sup>7</sup>  | 92                   |                                  | (ca. 31 - 186) <sup>7</sup> |   |                                |
| Tetrachloroethene                    | 100 <sup>2</sup>                   | trace – 590 | 50                              | 36.6 <sup>g</sup><br>(GSD 3.5)   |                              | 50                   | 28.9 <sup>g</sup><br>(GSD 2.9)   |                             |   | MUTTI et al. (1992)            |
| Tetrachloroethene                    | 7.9                                | 1 – 221     | 82                              |                                  | 89.7<br>(52.1 – 899)         | 19                   |                                  | 80.3<br>(58.0 – 135)        |   | VERPLANKE et al. (1999)        |
| Tetrachloroethene                    | 157                                | 9 – 799     | 16                              | 125 <sup>g</sup>                 | (49 – 535)                   | 13                   | 103 <sup>g</sup>                 | (32 – 254)                  |   | VYSKOCIL et al. (1990)         |
| Tetrachloroethene                    | 100 <sup>2</sup>                   | 0 – 950     | 192                             | 90 <sup>5</sup><br>(SD 310)      | 10 – 5690 <sup>5</sup>       | –                    | –                                | –                           | Low participation; no control group   | SOLET and ROBINS (1991)        |

| Main compounds  | Concentration (mg/m <sup>3</sup> ) |       | Total protein (mg/g creatinine) |                                  |                    |                      |                                  |                   | Remarks   | Reference               |
|---|------------------------------------|-------|---------------------------------|----------------------------------|--------------------|----------------------|----------------------------------|-------------------|---|-------------------------|
|   |                                    |       | Exposed workers                 |                                  |                    | Non-exposed controls |                                  |                   |   |                         |
|   | TWA                                | Range | No.                             | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)  | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |                         |
| Tetrachloroethene   | ca. 70 <sup>2</sup>                |       | 57                              | ca. 39 <sup>g</sup>              |                    | 80                   | ca. 42 – 46                      |                   | Values estimated from figures, two control groups | FRANCHINI et al. (1983) |
| Trichloroethene   | 80 <sup>2</sup>                    |       | 104                             | 57.7<br>(SD 20.4)                | (ca. 25 – 112)     | 102                  | 54.0<br>(SD 18.6)                | (ca. 17 – 125)    | Range estimated from figures                      | NAGAYA et al. (1989)    |
| Allyl chloride<br>epichlorhydrin<br>1,3-DCP<br>HCP <sup>3</sup> | < 3<br>< 1<br>< 2<br>< 0.25        |       | 73                              | 42.4                             | 39.9<br>(12 – 232) | 35                   | 58.2                             | 38.6<br>(8 – 255) |   | BOOGAARD et al. (1993)  |

| Main compounds                       | Concentration (mg/m <sup>3</sup> ) |       | Total protein (mg/l) |                                  |                               |                      |                                  |                        | Remarks  | Reference                      |
|--------------------------------------|------------------------------------|-------|----------------------|----------------------------------|-------------------------------|----------------------|----------------------------------|------------------------|--|--------------------------------|
|                                      |                                    |       | Exposed workers      |                                  |                               | Non-exposed controls |                                  |                        |  |                                |
|                                      | TWA                                | Range | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)             | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range)      |  |                                |
| Paint solvents<br>(used by painters) |                                    |       | 79                   |                                  | <b>43.1</b><br>(1.0 – 2282.0) | 104                  |                                  | 68.3<br>(10.0 – 725.0) | No measured solvent concentrations reported; TP sign. ↓ than in controls | ZSCHIE-SCHE and TRIEBIG (1990) |
| Paint solvents<br>(used by sprayers) |                                    |       | 103                  |                                  | <b>86.9</b><br>(1.0 – 434.0)  | 104                  |                                  | 68.3<br>(10.0 – 725.0) | No measured solvent concentrations reported                              |                                |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: TWA varied between 10 and 50 % of Swedish hygiene limit for toluene (300 mg/m<sup>3</sup>) and xylene (350 mg/m<sup>3</sup>)

2: values given in ppm in original reference

3: 1,3-dichloropropene: roughly equal mixture of Z/E-isomers

4: reported exposure level on average 0.5 x threshold limit values

5: In the original reference, values are given as unitless "albumin/creatinine ratios" which most likely correspond to g albumin/g creatinine

6: sum of hexanes at most workplaces exceeded TLV

7: values given as mg albumin/mmol creatinine in original reference; (MG creatinine: 113,12 g/mol)

**Tab. 9.8**  $\beta$ -glucuronidase ( $\beta$ Glu) activity in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds   | Concentration (mg/m <sup>3</sup> ) |       | $\beta$ Glu (U/g creatinine) |                                  |                   |                      |                                  |                   | Remarks   | Reference               |
|--|------------------------------------|-------|------------------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---|-------------------------|
|  |                                    |       | Exposed workers              |                                  |                   | Non-exposed controls |                                  |                   |   |                         |
|  | TWA                                | Range | No.                          | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |                         |
| Styrene  | ca. 215 <sup>2</sup>               |       | 51                           | ca. 12 <sup>g</sup>              |                   | 80                   | ca. 9 <sup>g</sup>               |                   | Values estimated from figures                     | FRANCHINI et al. (1983) |
| Toluene, xylene  | ca. 95 (toluene) <sup>2</sup>      |       | 118                          | ca. 14 <sup>g</sup>              |                   | 80                   | ca. 9 <sup>g</sup>               |                   | Values estimated from figures                     | FRANCHINI et al. (1983) |
| C <sub>5</sub> – C <sub>7</sub> aliphatics/cycloaliphatics, ethyl acetate, acetone | <sup>1</sup>                       |       | 182                          | 11.7 (SEM 1.2)                   |                   | 80                   | 13.6 (SEM 1.1)                   |                   | Hexanes concentration up to 800 mg/m <sup>3</sup> | MUTTI et al. (1981)     |
| Tetrachloroethene  | ca. 70 <sup>2</sup>                |       | 57                           | ca. 14 <sup>g</sup>              |                   | 80                   | ca. 9 <sup>g</sup>               |                   | Values estimated from figures                     | FRANCHINI et al. (1983) |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: sum of hexanes at most workplaces exceeded TLV;

2: values given in ppm in original reference.

**Tab. 9.9** Concentration of transferrin (TRF) in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds                  | Concentration (mg/m <sup>3</sup> ) |             | Transferrin ( $\mu\text{g/g}$ creatinine) |                                  |                   |                      |                                  |                   | Remarks   | Reference      |
|---------------------------------|------------------------------------|-------------|---|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|---|----------------|
|                                 |                                    |             | Exposed workers                           |                                  |                   | Non-exposed controls |                                  |                   |   |                |
|                                 | TWA                                | Range       | No.                                       | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |   |                |
| Petroleum naphtha               | 1619                               |             | 48  | 278 <sup>g</sup>                 | (41 – 2640)       | 23                   | 297 <sup>g</sup>                 | (33 – 2920)       | VYSKOCIL et al. (1991)  |                |
| Tetrachloroethene               | 100 <sup>1</sup>                   | trace – 590 | 50  | 359.2 <sup>g</sup><br>(GSD 2.8)  |                   | 50                   | 240.6 <sup>g</sup><br>(GSD 2.1)  |                   | High values (>15.4) more frequent in exposed group<br>MUTTI et al. (1992) |                |
| Not reported (refinery workers) | Not reported                       |             | 58  | 64.0                             |                   | 65                   | 109.0                            |                   | < 10 a production work  | GRUENER (1992) |
|                                 |                                    |             | 18  | 209.0                            |                   |                      |                                  |                   | > 10 a production work  |                |
|                                 |                                    |             | 42  | 86.0                             |                   |                      |                                  |                   | Maintenance staff   |                |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: values given in ppm in original reference.

**Tab. 9.10** Concentration of lysozyme in urine of solvent-exposed workers – results from cross-sectional studies

| Main compounds     | Concentration (mg/m <sup>3</sup> ) |          | Lysozyme (mg/g creatinine) |                                  |                   |                      |                                  |                   | Remarks                       | Reference               |
|--------------------|------------------------------------|----------|----------------------------|----------------------------------|-------------------|----------------------|----------------------------------|-------------------|-------------------------------|-------------------------|
|                    |                                    |          | Exposed workers            |                                  |                   | Non-exposed controls |                                  |                   |                               |                         |
|                    | TWA                                | Range    | No.                        | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) | No.                  | Mean <sup>a</sup><br>(SD or SEM) | Median<br>(range) |                               |                         |
| Toluene, xylene    | ca. 95<br>(toluene) <sup>2</sup>   |          | 118                        | ca. 5.8 <sup>g</sup>             |                   | 80                   | ca. 5.3 <sup>g</sup>             |                   | Values estimated from figures | FRANCHINI et al. (1983) |
| Styrene            | ca. 215 <sup>2</sup>               |          | 51                         | ca. 6.2 <sup>g</sup>             |                   | 80                   | ca. 5.3 <sup>g</sup>             |                   | Values estimated from figures | FRANCHINI et al. (1983) |
| Styrene            | 225                                | 83 – 366 | 37                         | 0.96<br>(SEM 0.23)               |                   | 35                   | 1.13<br>(SEM 0.20)               |                   |                               | VYSKOCIL et al. (1989)  |
| Petroleum naphtha  | 1619                               |          | 48                         | 0.51 <sup>g</sup>                | (0.1 – 5)         | 23                   | 0.58 <sup>g</sup>                | (0.09 – 2.25)     |                               | VYSKOCIL et al. (1991)  |
| Tetrachloro-ethene | ca. 70 <sup>1</sup>                |          | 57                         | ca. 6.6 <sup>g</sup>             |                   | 80                   | ca. 5.3 <sup>g</sup>             |                   | Values estimated from figures | FRANCHINI et al. (1983) |
| Tetrachloro-ethene | 157                                | 9 – 799  | 16                         | 0.56 <sup>g</sup>                | (0 – 4.16)        | 13                   | 0.15 <sup>g</sup>                | (0 – 1.49)        |                               | VYSKOCIL et al. (1990)  |

a: arithmetic mean, if not otherwise indicated

g: geometric mean; GSD: geometric standard deviation

1: values given in ppm in original reference.

## 9.2 List of abbreviations

|                 |  |
|-----------------|--|
| <b>AAP</b>      | Alanine aminopeptidase   |
| <b>ABM</b>      | Alveolar basement membrane   |
| <b>AGBM</b>     | Anti-glomerular basement membrane antibodies                             |
| <b>ALAB</b>     | Anti-laminin antibodies  |
| <b>ALB</b>      | Albumin  |
| <b>ARF</b>      | Acute renal failure  |
| <b>BB50</b>     | Brush-border and endothelial wall-specific antigens                      |
| <b>BBA</b>      | Brush-border antigen   |
| <b>BUN</b>      | Blood urea nitrogen  |
| <b>CRF</b>      | Chronic renal failure  |
| <b>CYP2D6</b>   | Cytochrome P450 IID6   |
| <b>DCVC</b>     | N-acetyl-S-(2,2-dichlorovinyl)-L-cysteine                                |
| <b>EDTA-ERA</b> | European Dialysis and Transplant Association, European Renal Association |
| <b>ESRD</b>     | End stage renal disease  |
| <b>FNU</b>      | Fibronectin in urine   |
| <b>GAG</b>      | Glycosaminoglycans   |
| <b>GBM</b>      | Glomerular basement membrane   |
| <b>GFR</b>      | Glomerular filtration rate   |
| <b>GN</b>       | Glomerulonephritis   |
| <b>GSD</b>      | Geometric standard deviation   |
| <b>GSTM1</b>    | Glutathione S-transferase $\mu$  |
| <b>GSTT1</b>    | Glutathione S-transferase theta  |
| <b>HA</b>       | Hippuric acid (urinary metabolite of toluene)                            |
| <b>hc</b>       | Hydrocarbon  |
| <b>HCBD</b>     | Hexachlorobutadiene  |

|   |   |
|---|---|
| <b>HCP</b>                                | Hexachlorocyclopentadiene                                       |
| <b>HF5</b>                                | Brush border and myocytes of renal arterioles specific antigens |
| <b>IAP</b>                                | Intestinal alkaline phosphatase                                 |
| <b>IgA</b>                                | Immunoglobulin A  |
| <b>IgG</b>                                | Immunoglobulin G  |
| <b>LAM</b>                                | Laminin   |
| <b>LAP</b>                                | Leucine aminopeptidase  |
| <b>LDH</b>                                | Lactate dehydrogenase   |
| <b>MABP</b>                               | Mean arterial blood pressure                                    |
| <b>MHA</b>                                | Methyl hippuric acids (urinary metabolites of xylenes)          |
| <b>MEK</b>                                | Methyl ethyl ketone (butanone)                                  |
| <b>MPA</b>                                | Microscopic polyangiitis  |
| <b>NAG</b>                                | N-acetyl- $\beta$ -D-glucosaminidase                            |
| <b>NAT-2</b>                              | N-acetyl transferase 2  |
| <b>NSAP</b>                               | Non-specific alkaline phosphatase                               |
| <b>NSAID</b>                              | Non-steroidal anti-inflammatory drugs                           |
| <b>OR</b>                                 | Odds ratio  |
| <b>PGE<sub>2</sub></b>                    | Prostaglandin E <sub>2</sub>                                    |
| <b>PGF<sub>1<math>\alpha</math></sub></b> | Prostaglandin F <sub>1<math>\alpha</math></sub>                 |
| <b>PGF<sub>2<math>\alpha</math></sub></b> | Prostaglandin F <sub>2<math>\alpha</math></sub>                 |
| <b>p.m.p.</b>                             | Patients per million population                                 |
| <b>PRF</b>                                | Progressive renal failure                                       |
| <b>RBC</b>                                | Red blood corpuscles  |
| <b>RBP</b>                                | Retinol binding protein   |
| <b>RPGN</b>                               | Rapidly progressive glomerulonephritis                          |
| <b>SD</b>                                 | Standard deviation  |



|                        |  |
|------------------------|--|
| <b>SEM</b>             | Standard error of mean                       |
| <b>SOD</b>             | Superoxide dismutase                         |
| <b>TCA</b>             | Trichloroacetic acid                         |
| <b>TCVC</b>            | N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine |
| <b>THG</b>             | Tamm-Horsfall glycoprotein (uromucoid)       |
| <b>TLV</b>             | Threshold limit value                        |
| <b>TNAP</b>            | Tissue non-specific alkaline phosphatase     |
| <b>TP</b>              | Total protein in urine                       |
| <b>TRF</b>             | Transferrin                                  |
| <b>TXB<sub>2</sub></b> | Thromboxane B <sub>2</sub>                   |
| <b>WG</b>              | Wegener's granulomatosis                     |
| <b>α<sub>1</sub>M</b>  | α <sub>1</sub> -microglobulin                |
| <b>β<sub>2</sub>M</b>  | β <sub>2</sub> -microglobulin                |
| <b>βGal</b>            | β-galactosidase                              |
| <b>βGlu</b>            | β-glucuronidase                              |
| <b>γGT</b>             | γ-glutamyl transferase                       |
| <b>3CNAC</b>           | N-acetyl-S-(cis-3-chloroprop-2-enyl)cysteine |
| <b>1,3-DCP</b>         | 1,3-Dichloropropene                          |