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reexistence of chronic tubular damage in cases of renal cell cancer fter long and high exposure to trichloroethylene

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bstract Substantially more cases of tubular damage ere found among renal cell carcinoma patients who ad been exposed to high levels of trichloroethylene ver many years than among renal cell carcinoma atients who had not been exposed to trichloroethyne. This supports the hypothesis (Goeptar et al. 1995) hat chronic tubular damage may be regarded as a necessary precondition for trichloroethylene to exert nephrocarcinogenic effect. The findings also indicate hat the urine protein patterns identified with SDS-'AGE may represent a valuable parameter for effect iomonitoring of persons exposed *to* high levels of richloroethylene over many years.

ey words Trichloroethylene · Renal cell cancer · ubular damage

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recent epidemiological study. published in *Archives f Toxicology* (Henschler et al. 1995). has described an creased incidence of renal cell cancer in industrial orkers in Germany who had been exposed to very igh levels of trichloroethylene over many years. point of the discussion was that the observations in posed humans were corroborated by mechanistic nsiderations of a glutathione-dependent toxification athway leading to reactive nephrotoxic *and* nephrocinogenic intermediates of trichloroethylene. This publication has promoted discussion on human rcinogenicity of trichloroethylene. A recent extensive view of the published data regarding toxicity and rcinogenicity of trichloroethylene has particularly ut forward the argument that in any *case*, chronic nal damage should always be a prerequisite for the development of renal cell cancer after exposure to trichloroethylene (Goeptar et al. 1995).

In the context of recognition of occupational diseases, 17 patients who had been exposed to high levels of trichloroethylene over many years and who later were diagnosed with renal cell cancer, have been assessed at our institute.

In all these patients, prenarcotic symptoms such as a feeling of drunkenness, dizziness, headache and drowsiness had occurred frequently in connection with their past occupational exposure to trichloroethylene. The workers often left the work area for short intervals to "recuperate" in fresh air. Typical occupational activities were degreasing of metal wares, production of rubber boxes for storage of batteries, welding of metal surfaces covered with trichloroethylene, cleaning and decreasing activities in the textile industry and cleaning of felts and sieves in cardboard machines. In a number of cases the workers were exposed to hot trichloroethylene vapours. The workers were exposed to trichloroethylene under unacceptable hygienic working conditions. In general, hoods, ventilating systems and protective gloves were not available.

Mean data of exposure of this group were: start of exposure 1959, duration of exposure 15.2 years. The mean time point of renal cell carcinoma diagnosis was 1990. The mean latency period was 30.4 years. The individual exposure data are available on request.

In order to investigate the frequency of pathologic protein excretion patterns in renal cell cancer patients not exposed to trichloroethylene or similar solvents, we examined 35 renal cell cancer patients from a large urological clinic. These hospital patients were selected from the hospital register of tumor patients. The postoperative period after nephrectomy due to renal cell cancer was comparable to that of the 17 trichloroethylene exposed patients.

A newly developed procedure was employed to differentiate the urinary protein patterns of the patients of both groups. This was SDS-polyacrylamide gradient

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Table 1 Distribution of urinary protein patterns indicating location of kidney damage among renal cell cancer patients (number of given)

Renal cell cancer patients (after nephrectomy)	Physiological data	Tubular damage			Mixed glomerular/tubular damage	Glomerular damage
		Severe	Average	Slight		
Occupationally exposed to trichloroethylene ($n = 17$)[a]	0	6	6	2	3	0
Not exposed to trichloroethylene ($n = 35$)[b]	18	5	3	4	4	1

[a] Patients involved in a compensation suit for recognition of an occupational disease caused by trichloroethylene
[b] Hospital cases of renal cell cancer without evidence of occupational exposure to trichloroethylene

electrophoresis (SDS-PAGE) using "Phast System" (Pharmacia, Freiburg), silver-staining and consecutive laser densitometry. In contrast to a quantitative determination of specific single serum proteins and of tubular enzymes excreted in the urine, this semi-quantitative method offers the advantage of a high-resolution separation between approximately 20 different urinary proteins according to their molecular size (Kierdorf et al. 1993). It is thus possible to differentiate between different pathological protein patterns in the excreted urine which indicate tubular, glomerular or mixed renal damage.

Determination and assessment of the urinary protein patterns of both groups of patients was always carried out by the same clinical nephrologist who had been involved in the development of the method. Analysis was carried out blind, without any knowledge of names or exposure status of the patients.

The results are presented in Table 1. Protein excretion patterns which indicate tubular damage in the remaining kidney were identified in all 17 of the examined renal cell cancer patients who had been exposed to high levels of trichloroethylene over many years. Six cases of severe tubular damage, six cases of moderate tubular damage, two cases of minor tubular damage and three cases of mixed glomerular/tubular damage were identified.

Thirty-five hospital patients without trichloroethylene exposure were also examined (Table 1). Eighteen of these patients showed normal protein excretion patterns. Tubular damage was identified in 12 patients. mixed glomerular/tubular damage was identified in four patients, and one patient showed glomerular damage.

Overall, a substantially lower prevalence of tubular damage was found among the non-exposed group of hospital patients with renal cell cancer than in renal cancer patients who had been occupationally exposed to very high concentrations of trichloroethylene. The occupational exposure to potentially nephrotoxic substances was ascribed as the cause of the tubular damage in the hospital patients, expect in one case. This patient had been exposed to perchloroethylene between 1971 and 1972 as a dry cleaner.

In general, the present data, although limited, are fully consistent with the concept that the reactive metabolite, *S*-(1,2-dichlorvinyl)-L-cysteine, induces nephrotoxicity and proteinuria (Davis et al. 1995) and with the concept (Goeptar et al. 1995) that development of chronic tubular damage should be regarded as prerequisite for induction of renal cancer by trichloroethylene.

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