LETTER TO THE EDITORS

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Renal cell cancer correlated with occupational exposure to trichloroethene

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Green and Lash (1999) commented, in a letter to the editor, on our paper reporting an increased incidence of renal cell cancer in workers exposed to high concentrations of trichloroethene over extended periods of time (Vamvakas et al. 1998). Unfortunately, because of irregular handling of the letter by the editorial management of the journal, we were not in a position to follow common practice, that is to respond immediately and in the same issue (see footnote).

We do not accept the statement at the outset of Green and Lash’s letter that significant methodological flaws make our results unreliable. Rather, we regard their criticism as unsubstantiated, for following reasons.

1. Selection of controls

Green and Lash state that we explicitly excluded as controls individuals who would have presented to the hospital from which the cases were recruited. In fact, we made no such statement; it is a figment of Green and Lash’s imagination. The procedure for recruiting cases and controls in our study takes account of the infrastructure of hospitals in the region. It is important to note that this is not an urban situation with a centralized service serving all medical needs. Instead, four smaller hospitals with various major disciplines combine to serve these needs. Therefore, it was mandatory to include all four hospitals in the recruitment of cases and controls. The hospital from which cases were recruited has no accident ward; thus, patients with renal cell carcinoma were recruited from the one hospital equipped to perform urological surgery, whereas accident victims were recruited from the other three hospitals serving the same population. Which hospital they were brought to depended on the location of the accident, on where there was a vacancy or on chance. In effect, cases and controls were recruited from the same population with the same rate of exposure to the factor under investigation: trichloroethene. There was no removal from the control series.

We support Green and Lash’s point that the selection of controls should always be viewed critically. The controls selected should have experienced the same rate of exposure to the factor studied, (trichloroethene in our case) as the population from which the cases arose (Schlesselman 1982). The removal from the control series of individuals with conditions known to predispose them to or against the exposure studied is common practice. The appropriate selection of controls has been the issue of a variety of papers (e.g. Miettinen 1985). The options include the use of patients with different diagnoses or accident victims. The latter have been used by Trichopoulos and colleagues, for example, in a series of studies (Kalantzi et al. 1996; Garidou et al. 1996) and the technique has also been described by MacMahon and Trichopoulos (1996). In order to ensure a similar response to the questionnaire, it seems preferable to select patients with a disease other than that of referents (e.g. Hernberg 1992). We used accident victims for several reasons: these patients undergo medical examinations to exclude the possibility of any renal disease more frequently than other patients, the reason for their being in the hospital seems to be unrelated to the exposure,
and it is most likely that these patients belong to the same study base as the controls and can be considered as a random sample.

2. Information obtained by interview

All interviews (cases and controls) were performed by the same physician (author L.M.), in some cases assisted by a second physician. The interviews took place at the hospitals. In some cases, where patients had died, the interviewer visited the nearest relatives and, if possible, obtained information about the level of exposure from former work-place colleagues.

3. Year of recruitment

The controls were interviewed in 1993, whereas the cases were those of patients who underwent nephrectomy between December 1987 and May 1992. The majority of cases (95%) had been diagnosed in 1989 or later. Green and Lash do not explain why this may introduce a bias. They may believe that the controls, being in the hospital in 1992 or 1 or 2 years earlier, would give different answers to questions about their occupation; a suggestion that we can not support. The distribution of workers with jobs in the metal-related industries is similar in both groups (26% compared to 28%). This high percentage is in accordance with figures from official population statistics, indicating that approximately 30% of all employees in that area are working in a metal-related industry. In this context, we wish to recall that, in the multinational study conducted by Mandel et al. (1995), among the men, only 10.8% of the cases and 6.1% of the controls had jobs in the iron and steel industry.

4. Different age distribution

We adjusted the odds ratio (OR) for this difference in various ways. First, in all age groups considered, the OR are above 1.0. If the analysis is restricted to persons older than 40 years, the OR overall is 6.6 (95% CI = 2.5–18.0), which is still statistically significant. The test for heterogeneity of the OR across the age categories leads to a non-significant result ($P = 0.7$). Green and Lash report a synergy index of 4.1 for those aged 50–60 years compared with those over 50 years, indicating a synergy between age and exposure. However, they do not follow common practice in also reporting the corresponding confidence interval, which, in our case ranges from 0.2 to 65.2. This wide interval reflects the uncertainty of a synergy index based on small numbers and furthermore a non-statistically significant deviation of the synergy index from 1.0. There are more recent techniques for investigating the interaction of various risk factors, e.g. the generalized additive model. The analysis also shows no interaction between age and exposure. Thus, the conclusions drawn by Green and Lash, that the effect of aging is dramatically overestimated and the effect of trichloroethylene may also be overestimated, can by no means be justified.

Scientific experience confirms that all epidemiological studies may raise some objections. In hospital-based case/control studies there can never be a complete assurance that a minor selection bias was not introduced. However, it is by no means justified to call this a serious methodological flaw as claimed by Green and Lash, insasmuch as they do not suggest, or provide better alternatives. Despite difficulties with our approach, there is paramount evidence for a causal relationship between high and long-term trichloroethylene exposure and the formation of renal cell cancer. First of all, the epidemiological studies performed by others, although ending up without statistical evidence of a positive correlation, do not contradict our findings for three reasons. (a) The majority of these authors investigated mortality. It is well established that, because of advanced diagnostic facilities and surgical treatment, high survival rates are achieved in nephrectomized patients, thus making morbidity a much more efficient indicator of the carcinogenic potential in humans (Coleman et al. 1993; LaVecchia et al. 1992); the latest report from the NCI (National Cancer Institute) shows a 5-year survival rate for kidney cancer of 56.3% (National Cancer Institute 1994). (b) Exposure doses are not well analysed in these studies; only in one investigation (Axelson et al. 1994), which is the only morbidity study, have reliable estimates of exposure doses been documented, the exposure concentration being just below 30 ppm (20 ppm average), whereas in our study the description of the work and reported objective symptoms substantiate a many-times higher exposure. (c) Several other studies have also shown a positive trend towards increased risk of renal cell cancer (e.g. Blair et al. 1998; Morgan et al. 1998; Dosemeci et al. 1999; Greiser and Molzahn 1997).

Furthermore, a variety of additional findings strengthen the biological plausibility of a causal relationship:

- The same localisation and type of tumour as observed in humans are encountered in experimental animals exposed to concentrations not much in excess of current workplace levels (200 ppm compared to 50 ppm; Maltoni et al. 1988), equalising or falling short of those prevailing in our cohort and case/control studies.
- Trichloroethylene produces, in rats as well as in mice, pathological lesions in the kidney that are regarded as obligatory preabstages of renal cell carcinomas; similarly acute trichloroethylene intoxication in humans produces the same pathological lesions (Brüning et al. 1999b).
- There is a well-established theory for the mechanism of nephrocarcinogenicity of trichloroethylene (Vamvakas et al. 1993), which is further strengthened by identical findings with the chemically and toxicologically closely related compounds tetrachloroethylene, hexachlorobutadiene and dichloroacetylene, all typically producing renal cell carcinomas in experimental animals.