

LETTER TO THE EDITOR

Phenoxy herbicides, chlorophenols, soft-tissue sarcoma (STS) and malignant lymphoma

Sir – Drs Smith and Christophers concluded that they did not find any association between exposure to phenoxy herbicides, chlorophenols and soft-tissue sarcoma (STS) and malignant lymphoma (Smith & Christophers, 1992). I feel, however, that their results must be interpreted with caution. Only 30 cases with STS, ten with Hodgkin's disease and 42 with non-Hodgkin lymphoma including one case of hairy cell leukaemia were interviewed. For each case one population control and one cancer control was used. The response rate was very low in the initial sample; only 70% for cases, 56% for cancer controls and 70% for population controls. Of the cases 80% were interviewed prior to 1986, vs 18% of the cancer controls. No population controls were interviewed prior to 1986. Differential recall bias on exposure and interviewer bias could thus have been introduced in the study. Furthermore, the interviewers were not blinded and there were 'administrative problems' in the study which were not described.

During the time period when the study was performed, especially when the population controls and most of the cancer controls were interviewed, there was an animated debate in Australia on potential adverse health effects, especially malignant diseases, from exposure to phenoxy herbicides, i.e., Agent Orange (Royal Commission, 1985; Monsanto Australia Limited, 1985; Axelson, 1986; Axelson & Hardell, 1986; Hardell & Axelson, 1986; 1989; Christophers, 1986).

Exposure to phenoxyacetic acids or chlorophenols gave a relative risk of 1.0 for STS and 1.5 for malignant lymphoma in the study of Drs Smith and Christophers. For those exposed more than 30 days the risk was doubled for STS and almost three-fold for malignant lymphoma. This may support an association, i.e., an effect of dose-response. The results were not statistically significant but the power of the study was limited due to the low number of cases and controls.

Malignant lymphomas, both Hodgkin's disease and non-Hodgkin's lymphoma, have been associated with exposure to phenoxy herbicides and chlorophenols in previous studies (Hardell *et al.*, 1981). For non-Hodgkin's lymphoma an association with phenoxy herbicides not contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has been shown (Hoar *et al.*, 1986; Hoar Zahm *et al.*, 1990). In our study 12 cases and one control were exposed to such phenoxyacetic acids. Regarding STS in our studies (Hardell & Sandstrom 1979; Eriksson *et al.*, 1981; Hardell & Eriksson 1988; Eriksson *et al.*, 1990) the subjects were in most instances exposed to the types of these chemicals which were contaminated with dioxins, both TCDD and other isomers.

Other studies have displayed conflicting results which has been reviewed (Lillienfeld & Gallo 1989; Eriksson *et al.*, 1990).

TCDD is carcinogenic in animals (Kociba *et al.*, 1978; Pitot *et al.*, 1980) which is also the case for hexa-CDD including an increased incidence of STS (NTP 1980; NTP 1989). Two recent studies have verified an association

Table I Mantel-Haenszel odds ratios (OR) and 90% confidence intervals (CI) for STS among persons exposed to all dioxins, TCDD, and dioxins other than TCDD in four case-control studies involving 434 cases and 948 controls. All subjects were exposed for at least one day and a minimum latency period of 5 years was used

	Unexposed	Exposed < 1 year	Exposed ≥ 1 year
<i>All dioxins</i>			
Cases	352	58	24
Controls	865	74	9
OR	1.0	2.4	6.4
CI	–	1.7–3.4	3.5–12
<i>TCDD</i>			
Cases	352	40	6
Controls	865	39	2
OR	1.0	3.0	7.2
CI	–	2.0–4.5	2.6–20
<i>Other dioxins</i>			
Cases	352	18	18
Controls	865	35	7
OR	1.0	1.7	6.2
CI	–	0.98–2.9	2.9–13

between exposure to phenoxy herbicides, chlorinated phenols or TCDD and STS in humans (Fingerhut *et al.*, 1991; Saracci *et al.*, 1991). In fact, a carcinogenic effect by TCDD, i.e. an effect on all cancer sites combined, has been shown in three studied cohorts (Zober *et al.*, 1990; Fingerhut *et al.*, 1991; Manz *et al.*, 1991).

In a meta-analysis of our four case-control studies on STS we found a dose-dependant increased risk associated with exposure to TCDD as well as other dioxins, i.e., assessed as exposure to phenoxy herbicides or chlorophenols contaminated with TCDD and other isomers, Table I (Hardell *et al.*, 1991). The result of the Mantel-Haenszel extension test for trend was significant for all strata ($P < 0.001$).

I believe that further studies on the etiology of STS and malignant lymphoma should include data on exposure to dioxins or dioxin contaminated chemicals. Little has come out from studies of workers with 'potential' exposure or job category, e.g., farming, taken as surrogate for exposure (Wiklund & Holm 1986; Wiklund *et al.*, 1988; Smith *et al.*, 1984). In fact, the results in several studies might have been blurred by the fact that exposure to chlorinated phenols and their derivatives never was assessed or that the method used was insensitive to assess such exposure.

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