Original article
Scand J Work Environ Health 1987;13(1):9-17
doi:10.5271/sjweh.2077

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Phenoxy herbicides and soft-tissue sarcomas in female rice weeders

A population-based case-referent study

by Paolo Vineis, MD,1 Benedetto Terracini, MD,1 Giovannino Ciccone, MD,1 Alessandro Cignetti,2 Eva Colombo,1 Adalberto Donna, MD,3 Lidio Maffi,1 Roberto Pisa, MD,4 Paolo Ricci, MD,5 Ermanno Zanini,3 Pietro Comba, DSc,6

VINIEIS P, TERRACINI B, CICCON E G, CIGNETTI A, COLOMBO E, DONNA A, MAFFI L, PISA R, RICCI P, ZANINI E, COMBA P. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders: A population-based case-referent study. Scand J Work Environ Health 13 (1987) 9–17. A population-based case-referent study was conducted in an area of northern Italy where rice growing is the predominant agricultural activity and phenoxy herbicides have been used since 1950. Manual rice weeding was formerly performed by a seasonal female working population; in the early 1950s these women were concurrently exposed to chemical herbicides. Sixty-eight persons representing incident and histologically revised cases (31 women) and 158 population referents (73 women) were interviewed. The cases were histologically confirmed independently by two blinded pathologists, and exposure to phenoxy herbicides was assessed by two blinded pesticide researchers. An age-adjusted odds ratio of 0.91 was found for the living men (with suspect exposures; no man diagnosed as a case had been exposed with certainty to phenoxy herbicides). Among the living women the relative risk was 2.7 (90% confidence interval 0.59–12.37), and it further increased when attention was restricted to women exposed in the whole 1950–1955 period and to younger age groups.

Key terms: case-control study, occupational exposure, rice growing.

Chlorinated phenoxy acids, namely, 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), 2,4-dichlorophenoxy acetic acid (2,4-D) and 2-methylchlorophenoxyacetic acid (MCPA), have been manufactured since the early 1940s and extensively used as herbicides in agriculture and forestry since the 1950s. A mixture of 2,4,5-T and 2,4-D (Agent Orange) was used as a defoliant during the Vietnam war.

An association between occupational exposure to phenoxy herbicides, both in their manufacture and use, and the subsequent occurrence of soft-tissue sarcomas has been suspected in some reports (2, 8, 9, 14, 18), but not confirmed by others (12, 27). A few studies have not been sufficiently informative (10, 21, 24, 26). (See also the reviews in references 1 and 6). The International Agency for Research on Cancer, chiefly on the basis of reports by Eriksson et al (8) and Hardell & Sandström (14), evaluated the evidence on the carcinogenicity of phenoxy acid herbicides to humans as limited (15).

Most of the aforementioned authors emphasized the need for further knowledge. Therefore we decided to undertake an investigation in the provinces of Vercelli, Novara, and Alessandria (northern Italy), where rice growing is the predominant agricultural activity. The total population in this area is approximately 1.5 million. Phenoxy herbicides were introduced in large amounts in the early 1950s and have been extensively used up to now. According to official statistics (16, 17), more than 4.8 t of 2,4-D and 21.7 t of MCPA were used in the three provinces in 1959 (data not available for 2,4,5-T). The corresponding figures for 1969 were 24.5 t for 2,4-D, 29.4 t for MCPA and 125.1 t for 2,4,5-T. 2,4,5-T was officially banned in 1970. Before the introduction of chemical herbicides, a female working population was seasonally engaged in rice weeding. For a period around 1950–1955 rice weeding was still done manually although chemical weeding was being experimented with. It is therefore reasonable to assume that the rice weiders working during this period were exposed to phenoxy herbicides, mainly through skin contact.

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Subjects and methods
Case identification and ascertainment

New cases of soft-tissue sarcoma with a proved or suspected histological diagnosis in 1981 – 1983 (age of person ≥ 20 years) were identified through all of the pathology departments of the three provinces (hospitals of Vercelli, Novara, Alessandria, Bergomanero, Biella, Casale Monferrato). The search was extended to six pathology departments in the city of Torino and to the National Cancer Institute in Milan, where residents in the three provinces could be referred for treatment. Overall, 135 potential cases were identified (116 in hospitals located in the three provinces and 19 in Torino or Milan). Visceral sarcomas were excluded.

Histological specimens (with the exception of the cases diagnosed in Torino and Milan and four other cases) were independently reviewed by two pathologists (AD, RP), blindly with respect to the exposure status and to previous diagnosis. The classification of the World Health Organization (WHO) was adopted for the soft-tissue sarcomas (7).

Of the 135 identified cases, 18 were excluded because the person’s town of residence was unknown or the person was not traced after five attempts (table 1). After the histological review, 26 cases were discarded. For five others the two pathologists agreed on the diagnosis of soft-tissue sarcoma but did not agree on the histological type. After a check of the clinical records, four cases turned out to be visceral sarcomas and were excluded. For nine histologically confirmed cases, we met with refusal to participate, and for two in which the subject was deceased no relative could be traced. Of the remaining 75 cases, 68 were incident (ie, newly diagnosed in 1981 – 1983), and seven turned out to be prevalent (ie, diagnosed prior to 1981) during a check of the clinical records. The seven prevalent cases were not included in the analyses. Of the 68 subjects remaining, 44 were living and 24 were deceased.

The age-standardized annual incidence rate (including interviewed and noninterviewed subjects and excluding prevalent and visceral cases) was 2.8/100 000 [95 % confidence limits (CL) 1.3–4.2] for the men and 2.0 (95 % CL 0.8–3.1) for the women (age ≥ 20 years). These rates do not take into account the histological revision in order to be comparable to the rates reported in 1976 – 1977 by the Cancer Registry of the Province of Varese (an area close to the study area). The latter rates (per 100 000, age ≥ 20 years) were 2.3 (95 % CL 0.4–4.1) for the men and 1.5 (95 % CL 0.06–2.9) for the women (23). (All the rates have been age-standardized on the basis of the world population.)

Living referents

A random sample of eligible referents (30 living men and 30 living women aged ≥ 20 years from each province) with a distribution, by municipality, representative of the population of each province was drawn from electoral rosters. The overall number of referents was approximately twice the expected number of eligible cases. In fact, a total of 168 individuals from 65 municipalities were identified versus 180 expected. (Four electoral offices did not respond at all, and a few offices provided a lower than required number of individuals, for a total of 12 losses.)

Deceased referents

Thirty-seven of the 135 persons originally enrolled as cases were deceased at the time of the interview. Therefore, for each of these 37 persons, two deceased individuals, to be matched to the deceased subject by age (± 4 years), sex, and year of death, were identified as referents from the same municipality as the deceased subject through the demographic offices of the municipalities. There was no selection of the cause of death, with the exception of the exclusion of one suicide (for ethical reasons).

Seventeen deceased subjects with soft-tissue sarcoma had two matched referents. Only one referent met the matching criteria for six cases. No individual with the corresponding requirements was found for five cases. The municipalities did not respond for eight referents. And, finally, no referent was sought for five persons with soft-tissue sarcoma because they were enrolled in the National Cancer Institute in Milan after the scheduled end of the study. A total of 40 deceased referents were therefore known for interview purposes, and in fact the relatives of 36 were interviewed.

Interviews

Each enrolled subject was given a code number unrelated to the nature of their case-referent status. All subsequent procedures until the final stage of the analysis were blind. Each living subject was mailed an invi-
tation to be interviewed, with no mention of the precise purpose of the study. Whenever possible, the invitation was followed by telephone calls in an attempt to schedule an interview date. Otherwise, additional letters inviting the individual to suggest a possible date for the interview were sent with a prepaid envelope inside. For each individual, at least five attempts (either by telephone or by a home visit by the interviewer) were made before the individual was considered untraceable. For deceased persons the next-of-kin was identified, and the same procedure was followed.

A simplified postal questionnaire was sent to subjects who, for any reason, refused a direct interview but agreed to provide information by mail. Overall, information on 16 cases and 37 referents was obtained in this way. The postal questionnaire was suitable for an exposure assessment identical to that provided by the direct interviews.

All the interviews were carried out by a trained interviewer (LM). The questionnaires collected (i) demographic information, (ii) a life-long smoking history, (iii) a life-long occupational history (including job titles, addresses of the plants or farms, and types of products or crops), (iv) a history of radiological therapeutic treatment, and (v) a history of residence changes, including a specific question on periods spent in rice-growing areas. In addition the questionnaire included a list of job titles potentially involving exposure to phenoxy herbicides or chlorophenols (including jobs in sawmills, the paper and leather industries, highway and railway maintenance, and flower and market gardening). Two additional sheets were filled out for those who had worked in agriculture, one for rice growing and one for other crops. In these sheets information was collected on the involvement in jobs entailing the handling, transportation, and distribution of herbicides; herbicide spraying procedures; other specific jobs involving (or not) herbicide exposure (ie, weeding and water regulation in rice growing); knowledge of exposure to herbicides (and more specifically to phenoxy acids or chlorophenols) or insecticides. This part of the questionnaire was prepared in cooperation with pesticide researchers.

Demographic information (including current occupation and educational level) for nonrespondents was collected from demographic offices of the municipalities of residence.

Assessment of exposure

Two experts with experience in chemical aspects of agriculture (EZ, AC) were asked to assess the exposure to phenoxy acids for each job recorded in the interviews. This assessment was done independently by the two and in a blind manner. The following criteria were used for reading and interpreting the questionnaires: category 1 = not exposed, category 2 = exposure could not be ruled out, and category 3 = certainly exposed. Attempts to distinguish between skin contact and other paths of exposure and between low and high levels of exposure proved not to be feasible. Rice weeding were considered to be exposed to phenoxy herbicides when they worked after 1950 and did not work exclusively in a small rice allotment of their own. Category 2 was used particularly for people engaged after 1950 in corn, wheat and pasture growing. As a first step, a separate exposure assessment was performed by each of the two experts. Subsequently, a joint assessment was made, in which they reached a common evaluation for each recorded job. The latter assessment was used in the analyses.

Herbicide spraying in the area has been chiefly done by tractor.

Coding of occupational histories

In addition to the aforementioned exposure assessment, all occupational histories were coded according to the classification for job titles of the International Labour Organization (4) and the United Nations classification for economic activities of plants or farms (22). All coding work was done by a single person (GC) in a blind manner.

Analyses

The analyses were performed with an HP-61 calculator using programs for epidemiology (25). Age-adjusted relative risks were computed according to Mantel-Haenszel's estimator (19); 90% confidence intervals were obtained with Miettinen's approximate procedure (20) (the lower limit of each interval corresponding to a 95% one-tailed confidence limit). In addition to age (in four groups), therapeutic X rays and smoking were included as potential confounders. The X-ray exposure represents a known risk factor for soft-tissue sarcoma (3), but there is no evidence of association with herbicide exposure. Smoking is not known to be a risk factor for this kind of tumor, but it was conservatively included as a potential confounder.

Results

Response and characteristics of the subjects

Table 2 reports the educational levels represented by the persons with soft-tissue sarcoma broken down into respondents and nonrespondents. The presented educational levels are those of the persons scheduled for interview (ie, the next-of-kin of deceased subjects). Responding men showed an unbalanced distribution for the cases and referents in the different educational categories (<6 years: 26 cases and 37 referents, ≥6 years: 10 cases and 43 referents; unknown: 1 case and 5 referents); the distribution of the women was more balanced (<6 years: 17 cases and 42 referents; ≥6 years: 12 cases and 30 referents; unknown: 2 cases and 1 referent).
Table 2. Educational levels (years of schooling) for the responding and nonresponding living subjects or the next-of-kin of deceased subjects. Nonresponding individuals include refusals, untraced individuals, individuals whose relatives were not identified, and individuals who had changed residence.

| Years of schooling | Living subjects | Next-of-kin of deceased subjects |
|-------------------|-----------------|---------------------------------|
|                   | Nonrespondents  | Respondents                      | Nonrespondents | Respondents |
|                   | Cases           | Referents                        | Cases          | Referents |
| < 6               | 10              | 18                               | 28             | 56        |
| ≥ 6               | 1               | 11                               | 14             | 65        |
| Unknown           | 5               | 13                               | 2              | 1         |

Table 3. Distribution of the living subjects by age group and exposure level (1 = not exposed, 2 = exposure could not be ruled out, 3 = exposed). Exposure refers to any calendar period. The number of subjects for whom information came from postal questionnaires is presented in parentheses.

| Age group (years) | Men     | Women   | Men     | Women   | Men     | Women   | Men     | Women   |
|-------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| < 55              |         |         |         |         |         |         |         |         |
| Category 1 Cases  | 7 (3)   | 5 (2)   | 6a (1)  | 1       | 1       | 6 (3)   | 1       | 1       |
| Category 1 Referents | 36 (8) | 36 (10) | 12 (2)  | 6 (2)   | 5       | 9 (5)   | 1       | 2       |
| Category 2 Cases  | 1 (1)   | -       | 1       | -       | -       | -       | 1       | (1)     |
| Category 2 Referents | 4      | 1       | 2       | 1       | -       | -       | 1       | -       |
| Category 3 Cases  | -       | -       | -       | -       | -       | -       | -       | -       |
| Category 3 Referents | 2      | 2       | -       | -       | -       | -       | -       | -       |

Table 4. Distribution of the living female subjects by age group and exposure level (1 = not exposed, 2 = exposure could not be ruled out, 3 = exposed). Only women exposed continuously during 1950–1955 have been included.

| Age group (years) | Category 1 Cases | Category 1 Referents | Category 2 Cases | Category 2 Referents | Category 3 Cases | Category 3 Referents |
|-------------------|------------------|----------------------|------------------|----------------------|------------------|----------------------|
| < 55              | 5                | 1                    | 6                | 4                    | 1                | 1                    |
| 55–64             | 36               | 6                    | 9                | 2                    | -                | -                    |
| 65–74             | -                | -                    | -                | -                    | -                | -                    |
| ≥ 75              | -                | -                    | -                | -                    | -                | -                    |

Among the men 26 (30.5%) of 85 referents and 15 (40.5%) of 37 subjects with soft-tissue sarcoma had worked in agriculture during at least some period of their worklife. The women with such occupations were 21 (28.5%) of 73 referents and 14 (45.5%) of 31 women with soft-tissue sarcoma. Two male referents and no men with soft-tissue sarcoma were assigned a job title code of rice grower. The respective numbers for the women were three and three (crude odds ratio 2.5). This code was the only job title code mentioning rice growing, and it was assigned when rice growing was the only activity performed in a given work period.

Living subjects

Table 3 reports the absolute numbers of living subjects with soft-tissue sarcoma and their referents by exposure levels and age groups for the two sexes. No men with soft-tissue sarcoma were definitely exposed, and exposure could not be ruled out for only two, the age-adjusted odds ratio being 0.91 (90% CL 0.21–3.91).

Among the alive women, four subjects with soft-tissue sarcoma and five of their referents were certainly exposed, and one and two, respectively, belonged to exposure category 2. This distribution corresponds to an odds ratio of 2.42 (90% CL 0.56–10.34) when exposure categories 2 and 3 are combined and an odds ratio of 2.70 (90% CL 0.59–12.37) for category 3 alone. The odds ratios were age-adjusted in the four age groups.

Table 4 shows the distribution of the living female subjects who were engaged in relevant jobs in the whole 1950–1955 period. Three with soft-tissue sarcoma and one referent met these criteria, all from exposure category 3. Unexposed were 16 women with soft-tissue sarcoma and 53 female referents, as shown in table 3.

Deceased subjects

Table 5 reports the age and exposure distribution for the deceased subjects. There were 24 next-of-kin of persons with soft-tissue sarcoma interviewed and 36 next-of-kin of referents. Three women and no men with soft-tissue sarcoma belonged to exposure category 3, and one woman and one man with soft-tissue sarcoma were classified into category 2. The odds ratio (age-adjusted in two age groups) for the women in exposure categories 2 and 3 was 1.05 (90% CL 0.21–5.1). When matched pairs or triplets were considered, there
Table 5. Distribution of deceased subjects by age group and exposure status. The number of subjects for whom information came from postal questionnaires is presented in parentheses.

| Exposure status | Age group (years) | Men | Women |
|-----------------|-------------------|-----|-------|
|                 | <55               | 5   | 1     |
|                  | 55–64             | 5   | 1     |
|                  | 65–74             | 2   | (1)   |
|                  | ≥75               | 1   | 3     |
| Unexposed Cases  |                   | 5   | 1     |
| Unexposed Referents |             | 5   | (4)   |
| Exposed Cases    |                   | 6   | 2     |
| Exposed Referents |                  | 5   | (2)   |
|                  |                   | 1   | 1     |
|                  |                   | 1   | 4     |
| Exposed a Cases  |                   | 2   | –     |
| Exposed a Referents |               | 2   | –     |
|                  |                   | 1   | –     |
|                  |                   | 3   | (1)   |

a Categories 2 (exposure could not be ruled out) and 3 (exposed) have been combined under this heading.

were only two: One was a triplet in which the subject with soft-tissue sarcoma and the two referents had been definitely exposed to phenoxy herbicides (category 3), and the second was a triplet in which one of the two referents (but not the sarcoma subject) belonged to category 3. Therefore a matched analysis of deceased female subjects was uninformative.

When the towns of residence of the deceased referents were compared with those of the living referents, important differences appeared. Six of the 23 deceased male referents lived in four towns of rice-growing areas versus 3 of 62 living referents. Among the women, 6 of 13 deceased referents lived in two towns with the same characteristics, versus 2 of 60 living referents. This comparison strongly suggests that overmatching of deceased subjects was introduced into the study by the inclusion of residence as a matching factor.

Confounding

Therapeutic X rays and smoking were considered as potential confounders. Overall, only two men and one woman with soft-tissue sarcoma, and one male and no female referents had been exposed to therapeutic radiation before 1981. Confounding by this variable, therefore, can be ruled out.

As for smoking, 24 (65%) of 37 men and 3 (11%) of 28 women with soft-tissue sarcoma, and one male and no female referents had been exposed to therapeutic radiation before 1981. Confounding by this variable, therefore, can be ruled out.

At smoking, 24 (65%) of 37 men and 3 (11%) of 28 women with soft-tissue sarcoma, and 21 (40%) of 52 female referents were smokers or exsmokers. (For two male referents information on smoking was not available.) These findings indicate a clear deficit of smokers among the women with soft-tissue sarcoma. Such a pattern can be interpreted as a consequence of the greater proportion of agricultural workers among the persons with soft-tissue sarcoma.

Histology and site of the sarcomas

Table 6 reports the distribution of the cases by histological type according to the WHO classification. Table 7 gives the histological type and site of the tumors for the exposed cases. Among the exposed women with soft-tissue sarcoma (categories 2 and 3 of exposure), there were two chondrosarcomas, two Kaposi sarcomas, two malignant fibrous histiocytomas, one chondrosarcoma, and one leiomyosarcoma. (One case was uncertain with respect to histological type.) No gross differences were noticed between the exposed and unexposed women with respect to the sites of the tumors. Their locations were as follows: head and neck (0 exposed/3 unexposed), retroperitoneal (1 exposed/2 unexposed), upper limbs (1 exposed/4 unexposed), lower limbs (3 exposed/7 unexposed), thorax (1 exposed/3 unexposed), abdomen (1 exposed/1 unexposed), pelvis (2 exposed/1 unexposed), site not specified (0 exposed/1 unexposed).

Table 6. Distribution of the interviewed incident histologically revised cases by histological type, according to the classification of the World Health Organization.

| Histological type                                | Men | Women |
|--------------------------------------------------|-----|-------|
| Dermatofibrosarcoma protuberans                   | 1   | –     |
| Liposarcoma                                       | 2   | 1     |
| Myxoid liposarcoma                                | 3   | 3     |
| Leiomyosarcoma                                    | 4   | 2     |
| Rhabdomyosarcoma                                  | 1   | 1     |
| Angiosarcoma                                      | 1   | –     |
| Malignant hemangio pericytoma                     | 1   | –     |
| Other vascular malignant tumors                   | –   | 1     |
| Synovial sarcoma                                  | 1   | 1     |
| Malignant schwannoma                              | 3   | 1     |
| Other malignant tumors of the peripheral nerves   | 2   | –     |
| Malignant tumors of nonchromaffin tissue          | –   | 1     |
| Chordoma                                          | –   | 1     |
| Chondrosarcoma of soft parts                     | 2   | 3     |
| Malignant giant cell tumor of soft parts          | 1   | –     |
| Malignant fibroxanthoma (malignant histiocytoma)  | 3   | 5     |
| Kaposi sarcoma                                    | 7   | 6     |
| Uncertain                                         | 1   | 4     |

a The original diagnosis of the five interviewed incident cases which were not reviewed were one dermatofibrosarcoma protuberans, one angiosarcoma, one malignant histiocytoma, and one Kaposi sarcoma among the men and one malignant schwannoma among the women. These cases were included in the analyses because of the confidence of the high level of the histological diagnosis. One of the men belonged to exposure category 2, while the others were unexposed.
Table 7. Sex, age, exposure category, job title, years of exposure, and histology and site of tumor (if a case) for the exposed subjects with soft-tissue sarcoma (cases) and the exposed referents.

| Case/referent status | Sex  | Age (years) | Exposure category | Job title                                  | Years of exposure | Histology and site of tumor                  |
|----------------------|------|-------------|-------------------|--------------------------------------------|-------------------|-------------------------------------------|
| Living case          | Female | 84         | 2                 | Rice weeder                                | Unknown           | Uncertain histology, lower limb            |
| Deceased referent    | Female | 71         | 3                 | Rice weeder                                | 1950 – 1963       | Kaposis, upper limb                        |
| Living case          | Female | 77         | 3                 | Rice weeder                                | 1950 – 1958       |                                            |
| Deceased referent    | Male   | 62         | 2                 | Farm laborer in rice growing               | 1950 – 1951       |                                            |
| Deceased referent    | Female | 84         | 3                 | Rice weeder                                | 1950 – 1961       |                                            |
| Deceased referent    | Male   | 86         | 2                 | Wheat, corn and pasture grower              | 1950 – 1974       |                                            |
| Deceased referent    | Male   | 43         | 3                 | Water regulator in rice fields             | 1954 – 1966       | Dermatofibrosarcoma protuberans, site unknown |
| Living case          | Female | 74         | 3                 | Rice weeder                                | 1950 – 1967       | Chondrosarcoma, lower limb                |
| Deceased referent    | Male   | 79         | 2                 | Wheat and corn grower                       | 1950 – 1971       |                                            |
| Deceased referent    | Female | 77         | 3                 | Rice weeder                                | 1950 – 1960       |                                            |
| Deceased referent    | Female | 79         | 3                 | Rice weeder                                | 1950 – 1970       |                                            |
| Deceased referent    | Female | 81         | 2                 | Corn and wheat grower                       | 1950 – 1967       |                                            |
| Deceased referent    | Male   | 62         | 2                 | Wheat, pasture and corn grower              | 1950 – 1970       |                                            |
| Living referent      | Male   | 54         | 2                 | Flower gardener                            | 1950 – 1984       |                                            |
| Living referent      | Female | 56         | 2                 | Corn and pasture grower                     | 1952 – 1984       |                                            |
| Deceased case        | Female | 79         | 2                 | Wheat and corn grower                       | 1950 – 1980       | Chordoma, pelvis                           |
| Living referent      | Male   | 47         | 3                 | Rice grower                                | 1960 – 1994       |                                            |
| Living referent      | Female | 52         | 3                 | Rice weeder                                | 1963 – 1968       |                                            |
| Living referent      | Female | 64         | 3                 | Rice weeder                                | 1960 – 1971       |                                            |
| Deceased case        | Male   | 44         | 3                 | Rice weeder                                | 1955 – 1968       |                                            |
| Living referent      | Male   | 88         | 2                 | Wheat and corn grower                       | 1950 – 1980       | Leiomyosarcoma, upper limb                |
| Living referent      | Female | 69         | 3                 | Rice weeder                                | 1955 – 1970       |                                            |
| Deceased case        | Female | 77         | 3                 | Rice weeder                                | 1950 – 1966       | Malignant fibrous histiocytoma, pelvis     |
| Living case          | Female | 73         | 3                 | Rice weeder                                | 1961 – 1963       | Chondrosarcoma, thorax                     |
| Deceased case        | Female | 84         | 3                 | Rice weeder                                | 1950 – 1960       | Kaposi, lower limb                         |
| Living case          | Male   | 64         | 2                 | Wheat and corn grower                       | 1960 – 1970       | Liposarcoma, head-neck                     |
| Deceased case        | Female | 62         | 3                 | Rice weeder                                | 1950 – 1978       | Malignant histiocytoma, retroperitoneal    |
| Living case          | Female | 75         | 3                 | Rice weeder                                | 1950 – 1970       | Leiomyosarcoma, abdomen                    |
| Living case          | Female | 60         | 3                 | Rice weeder                                | 1950 – 1963       |                                            |
| Living referent      | Female | 47         | 2                 | Market gardener                            | 1974 – 1984       |                                            |
| Living referent      | Female | 50         | 3                 | Wheat, corn and pasture grower              | 1970 – 1984       |                                            |
| Living referent      | Male   | 65         | 2                 | Wheat, corn and pasture grower              | 1975 – 1983       |                                            |
| Living referent      | Male   | 47         | 2                 | Wheat, corn and pasture grower              | 1978 – 1983       |                                            |

(continued)
Table 7. Continued.

| Case/referent status | Sex   | Age (years) | Exposure category | Job title                        | Years of exposure | Histology and site of tumor |
|----------------------|-------|-------------|-------------------|----------------------------------|-------------------|-----------------------------|
| Living referent      | Male  | 30          | 2                 | Wheat, corn and pasture grower    | 1967–1984         |                             |
| Living referent      | Male  | 47          | 2                 | Corn and pasture grower           | 1953–1957         |                             |
| Deceased referent    | Male  | 63          | 2                 | Wheat and corn grower\(b\)        | 1959–1984         |                             |
| Deceased referent    | Male  | 77          | 3                 | Farm laborer in rice growing      | 1950–1968         |                             |

\(a\) 2 = exposure could not be ruled out; 3 = exposed.
\(b\) Also engaged in railway maintenance (1953–1978).

Table 7 reports the ages at the time of the interview, vital status, job titles, years of start and cessation of exposure, and the level of exposure (as assessed by experts) for the exposed subjects, in addition to the histological types and tumor sites of those with soft-tissue sarcoma.

Exposure of persons with prevalent cases of soft-tissue sarcoma and those with visceral sarcomas

Of the five women interviewed who were considered to have prevalent cases of soft-tissue sarcoma, four were unexposed and one was definitely exposed, and they belonged to the 55- to 64-year age group. Two persons with visceral sarcoma were interviewed; they were both unexposed.

Discussion

Testing the hypothesis of an association between exposure to phenoxy acids in agricultural practice and soft-tissue sarcomas required a study to be carried out (i) on a population basis and (ii) in an area where phenoxy acids have been widely used. The present study meets both these requirements.

The most important exposures took place in the early 1950s, due to the concurrent presence of manual weedling and chemical spraying. Indeed, an increased risk of soft-tissue sarcoma was shown among the female rice weeders who had been employed in the early 1950s. Exposure among the men was negligible.

Although the present study is limited by a low power, on qualitative grounds our findings are consistent with both those obtained by Harddel & Sandström (14) and Eriksson et al (8) in similar population-based studies and with those of reports on small series of cases among workers exposed to chlorophenols and/or their derivatives in the chemical industry (9, 18).

Studies failing to suggest an association either (i) selected referents from cancer patient files (2) or adopted an approach involving proportional mortality ratios, which implied some loss in sensitivity (10, 21), or (ii) used a crude categorization of exposures, in terms of occupation at the time of the interview, vital status, job titles, years of start and cessation of exposure, and the level of exposure (as assessed by experts) for the exposed subjects, in addition to the histological types and tumor sites of those with soft-tissue sarcoma.

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Although the present study is limited by a low power, on qualitative grounds our findings are consistent with both those obtained by Harddel & Sandström (14) and Eriksson et al (8) in similar population-based studies and with those of reports on small series of cases among workers exposed to chlorophenols and/or their derivatives in the chemical industry (9, 18).

Studies failing to suggest an association either (i) selected referents from cancer patient files (2) or adopted an approach involving proportional mortality ratios, which implied some loss in sensitivity (10, 21), or (ii) used a crude categorization of exposures, in terms of occupation at the time of the interview, vital status, job titles, years of start and cessation of exposure, and the level of exposure (as assessed by experts) for the exposed subjects, in addition to the histological types and tumor sites of those with soft-tissue sarcoma.

Exposure of persons with prevalent cases of soft-tissue sarcoma and those with visceral sarcomas

Of the five women interviewed who were considered to have prevalent cases of soft-tissue sarcoma, four were unexposed and one was definitely exposed, and they belonged to the 55- to 64-year age group. Two persons with visceral sarcoma were interviewed; they were both unexposed.

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Table 8. Distribution of living female subjects by age group, exposure category, and educational level.*

| Age group (years) | <55 | 55–64 | 65–74 | ≥75 |
|------------------|-----|-------|-------|-----|
| Length of schooling | Unexposed | Exposed<sup>b</sup> | Unexposed | Exposed<sup>b</sup> | Unexposed | Exposed<sup>b</sup> | Unexposed | Exposed<sup>b</sup> |
| <6 years<sup>c</sup> | Cases | 1 | 1 | 3 | 1 | 1 | 1 |
| | Referents | 12 | 2 | 5 | 3 | 7 | 1 |
| ≥6 years | Cases | 4 | -- | -- | 3 | -- | 1 |
| | Referents | 24 | 1 | 1 | -- | 2 | -- |

* There are two values missing.
<sup>b</sup> Categories 2 (exposure could not be ruled out) and 3 (exposed) are combined under this heading.
<sup>c</sup> Age-adjusted odds ratio: 3.86 (90% confidence limits 0.87–17.15).

early 1950s may have been diagnosed before 1981, when our study started.

2. Elderly women (≥75 years) were less likely to be engaged in highly-exposing jobs in the 1950s, since they were already 45 years of age or older in that period. Their inclusion in the study may have introduced an underestimation of the risks.

3. The procedure of matching deceased referents to the deceased persons with soft-tissue sarcoma with respect to town of residence may have artifically raised the proportion of exposed referents. The proportion of definitely exposed women was similar among the deceased (3 of 10) and living (4 of 21) women with soft-tissue sarcoma but quite different among the deceased (5 of 13) and living (5 of 60) referents. The choice of a group of living referents, extracted from the general population, for comparison with the deceased subjects inducted as cases is considered to be the best option in case-referent studies; the only flaw is the quality of the interview, obtained from the next-of-kin of deceased subjects (5, 11). If we compare all of the female subjects with soft-tissue sarcoma (living + deceased) with the living referents only, the age-adjusted odds ratio is 2.71 (90% CL 0.51–14.17). We intend, in any case, to select another reference group of deceased individuals, unmatched to the subjects with soft-tissue sarcoma in respect to town of residence.

In conclusion, our study showed an odds ratio of 2.7 for living women who were exposed to phenoxy herbicides in any period of their life. When we restricted our attention to living women less than 75 years of age and exposed in the 1950–1955 period, an age-adjusted odds ratio of 15.5 (90% CL 1.3–180.3) was determined (table 4). When exposure to phenoxy herbicides among living females who had a regular job in agriculture (i.e., excluding unexposed nonagricultural workers) was analyzed, the age-adjusted odds ratio (Mantel-Haenszel) for exposure category 3 was 3.0.

The number of definitely exposed subjects with soft-tissue sarcoma and referents was negligible among the men. There is no specialized job such as pesticide applicator in rice growing in Piedmont, and annual herbicide spraying is performed, among numerous other jobs, by unspecialized rice growers or farm laborers. No dose-response relationship could be considered because we were not able to distinguish between high and low levels of exposure in the exposure assessment (with the exception of the a priori hypothesis concerning the 1950–1955 period). Most of the exposed subjects (both those with soft-tissue sarcoma and the referents) had been employed in rice weeding for more than 10 years (table 7).

Acknowledgments
This research was supported by Regione Piemonte (Ricerca biomedica finalizzata) and by CSI-Piemonte. In addition G Ciccone received a fellowship from the Associazione Italiana per la Ricerca sul Cancro.

We thank also Professor B Giau (Istituto di Economia Agraria, Università di Torino) for his skilled advice and the heads of the pathology departments of the hospitals of Biella, Novara, Vercelli, Borgomansero, Casale Monferrato and of the National Cancer Institute in Milan for access to their files and the submission of histological slides.

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Received for publication: 21 January 1986