Aims: To investigate the association between occurrence of soft tissue sarcomas (STS) in Mantua and residence near an incinerator of industrial wastes.

Methods: Cases were subjects with histologically confirmed primary malignant STS diagnosed 1989–98 in the population resident in Mantua and in the three neighbouring municipalities. Controls were randomly extracted from population registries, matched for age and sex. Residential history was reconstructed for all study subjects since 1960. Main residence was geographically positioned according to GPS standards.

Results: The study included 37 STS cases (17 men and 20 women) and 171 controls. The incidence of STS in the area of study was estimated as 8.8 per 100 000 in men and 5.6 per 100 000 in women. The odds ratio associated with residence within 2 km, standardised by age and sex, was 31.4 (95% CI 5.6 to 176.1), based on five exposed cases. At greater distances, risk rapidly decreased, showing a fluctuation around the null value of 1.

Conclusion: The study shows a significant increase in risk of STS associated with residence within 2 km of an industrial waste incinerator; an aetiological role of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) can be hypothesised.

METHODS

The city of Mantua and the three neighbouring municipalities of Roncoferraro, Virgilio, and San Giorgio (fig 1) constituted the study area. Mantua is a city of 51 300 inhabitants. The overall population of the three neighbouring municipalities is 21 800 people. The area is characterised by being flat and rich in water. Fog is quite frequent, while winds are moderate, with an a prevailing east-west direction.

The industrial area of Mantua, located southeast of the town, includes a large chemical plant, an oil refinery, a paper industry, and a mechanical plant. The chemical plant has been producing styrene from benzene since 1956; dichloroethane and chlorosoda were also produced. The incinerator of industrial wastes operated between 1974 and 1991. It could process 100 kg/h of liquid wastes and 750 kg/h of solid wastes. Its temperature could reach 950°C. In the years 1974–91 the incinerator treated process water, exhaust solvents, tars, pitches, exhaust resins, sludges, plastics, paper, glues, varnishes, pharmaceutical drugs, veterinary products, cosmetics, hospital wastes, and miscellaneous waste products from the farming and food industries. The majority of these wastes were classified as toxic. The chimney was 30 m high and had a diameter of 1.20 m; the emission rate was about 30 000 cubic metres per hour. After 1991, the activity of the incinerator underwent a major reduction.

Abbreviations: CI, confidence interval; GPS, global positioning system; NOS, no other specification; OR, odds ratio; PCDDs, polychlorodibenzodioxins; PCDFs, polychlorodibenzofurans; STS, soft tissue sarcomas; TCDD, tetrachlorodibenzo-p-dioxin
According to a recent survey, emissions from the industrial area and urban pollution "stagnate" over the whole Mantua area for most of the year, especially during the cold season.

Although no data on TCDD levels in environmental or biological matrices are available, it is apparent that the incinerator was for many years a potential source of dioxin release into the environment.

In order to evaluate the association between residence in the neighbourhood of the incinerator and occurrence of STS, a case-control approach was adopted.

The survey was carried out for the period 1989–98, the most recent decade for which information on cases was available. Cases were adult subjects with histologically confirmed primary malignant STS originating in non-visceral and visceral locations, retrieved from the pathology archives and hospital admission/discharge records from all of Lombardy and pathology files from hospitals located in parts of Venetia and Emilia regions) rendered the survey exhaustive. For each subject the following information was collected: age, sex, year of diagnosis, site and histological type of the tumour, vital status, and the date of death. The case ascertainment procedure did not include revision of the slides, but the actual pathology reports were scrutinised in detail.

The analysis of STS risk and distance from the incinerator was performed using rings of 1 km radius; the first ring had a radius of 2 km because a large part of the area was inside the industrial area, and no one was obviously residing there.

The present study was triggered by a previous report of a cluster of STS cases around the Mantua industrial area. The time window of the two studies was different, and only one case met the admissibility criteria of both studies. Analysis was thus performed, both including and excluding that case.

### RESULTS

The study includes 37 STS cases (17 men and 20 women), aged 26–85 years, and 171 controls (82 men and 89 women), aged 24–90 years. The mean age of cases (at diagnosis) and of controls (at recruitment) was, respectively, 60.9 (14.8) and 59.9 (15.7).

Sixty five per cent of the STS cases were non-visceral, with a predominance of male subjects, while among visceral cases the proportion of women was higher (table 1).

The annual incidence of soft tissue sarcomas in the area of study was estimated as 5.0 per 100 000 in men and 5.1 per 100 000 in women.

The association between occurrence of soft tissue sarcoma and distance of main residence from the incinerator was evaluated by logistic regression; the odds ratio associated with residence within 2 km, standardised by age and sex, was 31.4 (95% CI 5.6 to 176.1), based on five exposed cases (tables 2 and 3). At greater distances, risk rapidly decreased, showing a fluctuation around the null value of 1. When the distance of the main residence from the incinerator was considered as a continuous variable, a non-significant decrease in risk with.

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### Table 1 Distribution of 37 STS cases residing in the study area according to histology, gender, and site

<table>
<thead>
<tr>
<th>Morphology</th>
<th>ICD-O* code</th>
<th>Non-visceral sites</th>
<th>Visceral sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Sarcoma, NOS†</td>
<td>8800/3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Spindle cell sarcoma</td>
<td>8801/3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>8810/3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Fibromyxosarcoma</td>
<td>8811/3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>8830/3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>8832/3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Myxosarcoma</td>
<td>8840/3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Liposarcoma, NOS†</td>
<td>8850/3</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Liposarcoma, well differentiated</td>
<td>8851/3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Liposarcoma, myxoid</td>
<td>8852/3</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Leiomyosarcoma, NOS†</td>
<td>8890/3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9120/3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Uterus (3), stomach (1), ileum (2).</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>§Lung.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>¶Stomach (1), thyroid (1).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†NOS, no other specification.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>††Uterus.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

*ICD-O, International Classification of Diseases for Oncology.16
†NOS, no other specification.
‡Uterus.
§Lung.
¶Stomach (1), thyroid (1).
**Uterus (3), stomach (1), ileum (2).
†Breast.

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**Uterus (3), stomach (1), ileum (2).**

---

**Uterus (3), stomach (1), ileum (2).**

---

**Uterus (3), stomach (1), ileum (2).**
increasing distance was observed (OR 0.90; 95% CI 0.73 to 1.1). Of the five cases who lived within 2 km from the incinerator, one male patient affected by dermatofibrosarcoma protuberans had previously been employed as a chemical worker in the Mantua plant, while four female patients (two cases of liposarcoma and two cases of leiomyosarcoma) had not been employed in the plant. Removing the chemical worker from the analysis caused a small decrease of the association which maintained statistical significance (OR 25.1; 95% CI 4.2 to 150.8).

**DISCUSSION**

Before a critical evaluation of the study findings, some comments on validity issues are needed. The first question to be addressed is the case definition. The diagnosis of STS is quite complex because of the overlapping of some morphological aspects of these tumours with other neoplasms and because of their heterogeneity. No panel revision of the original specimen was feasible, but clinical records and pathological reports were thoroughly reviewed and checked. It is well known that the histological classification of STS includes hundreds of variants. The 37 cases of STS identified in Mantua during the study period belonged to 11 histological variants. Soft tissue sarcomas are a highly heterogeneous group of tumours and their exact pathogenesis is still unknown. The epidemiological association between STS and exposure to chlorophenols and phenoxyacids concerns the whole nosological entity, with no other histogenetic specification.

The second aspect of the study design that needs to be discussed is the assessment of exposure. In the absence of an exposure categorisation based on environmental monitoring of dioxin, it seemed reasonable to suspect a possible causal connection. As diet is the main route of exposure for dioxins, this hypothesis subsumes contamination of soil and food chain over the years and will have to be adequately tested.

With regard to possible confounding variables, they should both be associated with distance from the incinerator, and causally related to STS occurrence. Phenoxy herbicides do not meet this definition, since no major farming takes place in the neighbourhood of the industrial area of Mantua and no other hypothesised confounding variable seems to be supported by available evidence. The majority of cases in this study were resident in the town of Mantua (fig 1) as could be predicted by population density. The hospital incinerator was suggested as possible source of TCDD emission in the central part of the town, but spatial analysis did not show any trend of risk with distance from the hospital.

A sharp drop off in the effect of distance from the incinerator was apparent in this study, although there was no continuous trend. This observation is consistent with a localised increase in exposure patterns, that did not extend to the urban setting (fig 1). This hypothesis requires confirmation or refutation from environmental and biological monitoring.

The main finding of the present paper is an increased occurrence of STS in the population living closest to the industrial incinerator. Emissions of a large industrial area like the one in Mantua include volatile organic compounds, heavy metals, polycyclic aromatic hydrocarbons, and chlorinated compounds such as PCDDs and PCDFs. Evidence of an association with STS is so far available for dioxins, but not for most of the other aforementioned compounds; since dioxins can be emitted from incinerators, it seemed reasonable to suspect a possible causal connection. As diet is the main route of exposure for dioxins, this hypothesis subsumes contamination of soil and food chain over the years and will have to be adequately tested.

Prior to this report, almost all epidemiological studies on soft tissue sarcomas investigated occupational exposure to dioxin contaminated agents. One study from Finland reported

**Table 2** STS risk and distance of main residence from incinerator

<table>
<thead>
<tr>
<th>Distance of the main residence from the incinerator (km)</th>
<th>Cases (n)</th>
<th>Controls (n)</th>
<th>OR*</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>5</td>
<td>1</td>
<td>31.4</td>
<td>5.6 to 176.1</td>
</tr>
<tr>
<td>2-3</td>
<td>3</td>
<td>26</td>
<td>0.7</td>
<td>0.2 to 3.1</td>
</tr>
<tr>
<td>3-4</td>
<td>11</td>
<td>57</td>
<td>1.2</td>
<td>0.4 to 3.4</td>
</tr>
<tr>
<td>4-5</td>
<td>11</td>
<td>43</td>
<td>1.6</td>
<td>0.6 to 4.5</td>
</tr>
<tr>
<td>&gt;5</td>
<td>7</td>
<td>44</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*OR, odds ratio, adjusted by age and gender.
†CI, confidence interval.

**Table 3** Description of the five STS cases residing within 2 km of the incinerator

<table>
<thead>
<tr>
<th>Gender</th>
<th>Distance from the incinerator (km)</th>
<th>Histology Anatomical site</th>
<th>Previous employment in the Mantua chemical plant</th>
<th>Year of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.35</td>
<td>Dermatofibrosarcoma protuberans Thorax, skin</td>
<td>Yes</td>
<td>1996</td>
</tr>
<tr>
<td>Female</td>
<td>1.36</td>
<td>Liposarcoma myxoid Stomach</td>
<td>No</td>
<td>1993</td>
</tr>
<tr>
<td>Female</td>
<td>1.78</td>
<td>Leiomyosarcoma, NOS* Stomach</td>
<td>No</td>
<td>1990</td>
</tr>
<tr>
<td>Female</td>
<td>1.81</td>
<td>Liposarcoma myxoid Stomach</td>
<td>No</td>
<td>1996</td>
</tr>
<tr>
<td>Female</td>
<td>1.97</td>
<td>Leiomyosarcoma, NOS Uterus</td>
<td>No</td>
<td>1993</td>
</tr>
</tbody>
</table>

*NOS, no other specification.
an increase in mortality from soft tissue sarcomas in the population living in a district where drinking water contained 70–140 mg/l of chlorophenols due to leakages into the water from a wood industry. The aforementioned French study provided a standardized incidence ratio of 1.44 (p = 0.04) for residence around the incinerator of solid urban waste.

In the Seveso area, after accidental TCDD release in 1976, no death from STS was detected in the most severely affected A and B zone (0.8 expected), while four deaths occurred in the highly populated, less affected R zone (4.8 expected) from 1977 to 1996.25

To our knowledge, this is the first reported case-control study showing an increased risk of soft tissue sarcoma in a population potentially exposed to dioxins because of residence in the neighbourhood of an industrial waste incinerator. A survey of dioxin concentrations in various matrices in the study areas is in progress.

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