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No evidence of increased risk of soft tissue sarcomas in the neighborhood of a steel foundry in Verona

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Summary. The aim of the present study was to evaluate the possible association between occurrence of soft tissue sarcomas in Verona (Italy) and residence near a steel foundry, whose emissions of dioxin-like compounds may be relevant. Exposure to total suspended particulate (TSP) emitted from the plant as estimated by ADMS-urban dispersion model was used as an indirect index of exposure to dioxin-like compounds. Verona municipality was divided in six subareas according to the decreasing levels of estimated TSP exposure, and soft tissue sarcomas cases were mapped according to residence at time of diagnosis. Standardized incidence ratios were computed. No statistically significant departures between observed and expected cases were detected as illustrated by trend-test results.

Key words: sarcoma, dioxins, environmental exposure, epidemiology.

Riassunto *(Assenza di rischio osservabile di sarcomi dei tessuti molli in prossimità di una fonderia a Verona)*. Lo scopo dello studio è stato di valutare la possibile associazione tra l'incidenza dei sarcomi dei tessuti molli a Verona (Italia) e la residenza in prossimità di una fonderia le cui emissioni di sostanze diossino-simili possono essere rilevanti. L'esposizione al particolato sospeso totale (TSP) emesso dalla fonderia, stimato secondo il modello di dispersione ADMS-urban, è stato usato come un indicatore indiretto dell'esposizione alle sostanze diossino-simili. Il comune di Verona è stato suddiviso in sei sottoaree secondo i livelli decrescenti di esposizione stimati tramite il TSP e i casi di sarcomi dei tessuti molli sono stati mappati secondo la residenza al momento della diagnosi. Sono stati stimati i tassi standardizzati di incidenza. Non è stato osservato uno scostamento significativo tra gli osservati e gli attesi come dimostrato dai risultati del trend-test.

Parole chiave: sarcoma, diossine, esposizione ambientale, epidemiologia.

INTRODUCTION

Dioxin-like compounds (DLCs) are a heterogeneous group of chemicals including 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), other polychlorodibenzo-*p*-dioxins (PCDDs), some polychlorodibenzofurans (PCDFs) and polychlorobiphenyls (PCBs). Of the dioxin-like compounds, the tetrachlorodibenzo-*p*-dioxin is considered the most toxic. DLCs are products or by-products of industries or combustion processes characterized by a high persistency in the environment and by a long-lasting accumulation in human tissues and biological fluids. Main sources of DLCs are production of chlorinated herbicides, bleaching of paper, and waste incineration; high levels of PCDDs are also emitted from metallurgical industries including copper smelters, electric furnaces in steel mills, and wire reclamation incinerators [1].

A wide range of adverse health effects of DLCs has been reported in humans [2-4]. With regard to carcinogenic risk, TCDD has been evaluated by the International Agency for Research on Cancer as a human carcinogen [5]. The EPA [6] recommended the implementation of further epidemiological studies on DLCs exposed populations, in order to better evaluated the health risk for human.

The purpose of the present paper is to test the hypothesis of an increased occurrence of soft tissue sarcomas (STS) in the neighbourhood of a steel foundry, based on two assumptions: an increased risk of STS has been reported in populations living near some industrial plants characterized by the emission of dioxin-like compounds, such as incinerators [7-9], while no *ad hoc* studies focused on steel foundries have so far been published, even if the amount of DLCs released by these facilities may be noteworthy [1].

The adopted study design is a micro-geographic approach based on the estimation of incidence rates of STM in the sub-areas of Verona municipality charac-

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terized by decreasing levels of exposure to the foundry's plume. Individual assessment of cases is coupled with ecological estimation of exposure, thus resulting in a "semi-indivudual" approach as defined by Künzli and Tager [10].

MATERIALS AND METHODS

The foundry

The "second casting" steel foundry at study is located in the city of Verona (Italy), where it operates since about one hundred years. Annual steel production increased from 472 000 tons in 1991 to about 800 000 tons in 2000-2004.

The production cycle can be summarized as follows: scrap steel is loaded in electrical arc furnaces and subsequently smelted, refined, and casted. Fumes, in order to be abated, are capped both during loading and smelting phases. Emissions in the atmosphere occur from two chimney-stalks located in the smelting department. Both stalks are 30 m high with a section of 21 square meters. Fume temperature is 70 °C and fume speed is 11 m/s.

In 1991 total particulate matter emissions reached 17.3 kg/h; they decreased to about 1.5-3.0 kg/h subsequently to the installation of new abatement systems during the Nineties. In the period from November 2002 through March 2003 the dispersion of the total suspended particulate (TSP) from the two chimney-stalks was respectively of 2.0 mg/Nm^3 and 1.4 mg/Nm^3 [11].

Exposure data

In the absence of an *ad hoc* environmental monitoring system, an indirect procedure for the assessment of exposure was based on the distribution of daily average total suspended particulate emitted from the two chimneys in the period from November 2002 through March 2003 and estimated according to the ADM-Urban dispersion model. These data were provided by the Venetian Region Environmental Protection Agency [11]. According to the model, the territory of Verona municipality can be divided in six areas characterized by decreasing levels of TPS concentration caused by the foundry's emission *(Figure 1)*. The first two areas (TSP concentration > 0.075 and 0.06-0.075 μg/m^3 respectively) correspond to the location of the industrial setting and have no resident population.

The cases

The survey was carried out for the period from 1 January 1990 through 31 December 2003. Cases were adults (age > 19 years) with a first-incident histologically confirmed diagnosis of malignant soft tissue sarcoma, originating in non-visceral and visceral locations, retrieved from the pathology archives and hospital admission/discharge forms recorded at the Local Health Authority and for the only years 1990-1996, from the Venetian Region Cancer Registry. Inclusion criteria were based on the histological classification of soft tissue tumours of Weiss and Goldblum [12], which

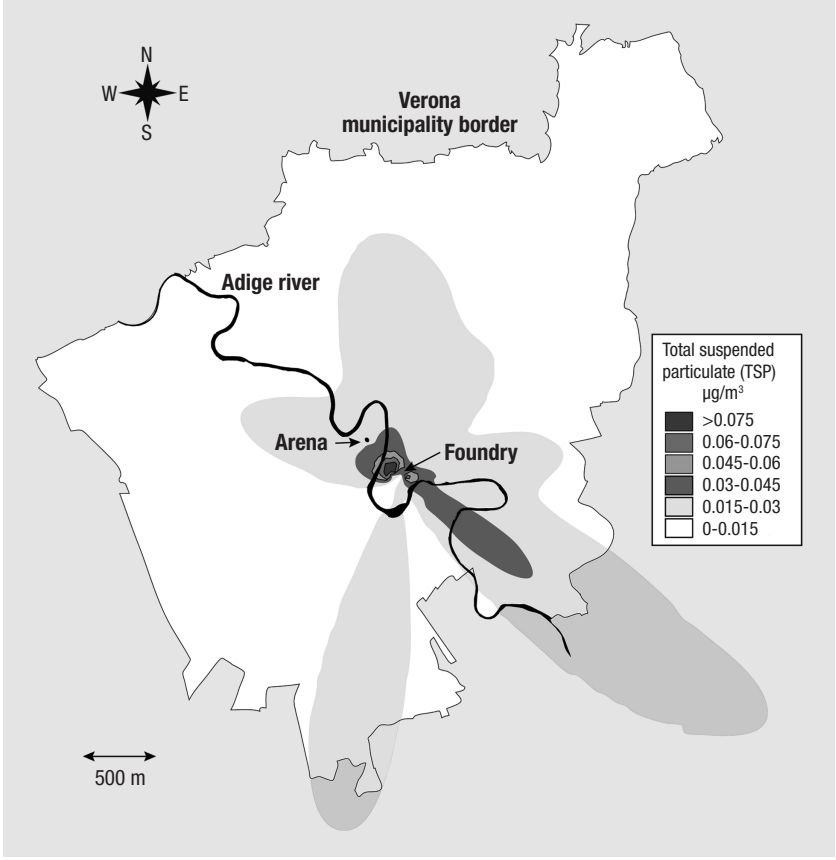

Fig. 1 | *Total suspended particulate (TSP) concentration in the six subareas of Verona municipality. TSP: daily average from November 2002 through March 2003.*

Table 1 | *Soft tissue sarcoma distribution according to histology, site, and gender*

Morphology	ICDO-3[a] code	Non visceral sites		Visceral sites		Total
		Men	Women	Men	Women	
Sarcoma, NOS[b]	8800/3	7	10	4	8	29
Spindle cell sarcoma	8801/3	1	1	2	-	4
Fibrosarcoma, NOS[b]	8810/3	1	2	-	2	5
Malignant fibrous histiocytoma	8830/3	7	-	-	-	7
Dermatofibrosarcoma protuberans	8832/3	8	13	-	-	21
Myxosarcoma	8840/3	1	-	-	-	1
Liposarcoma, NOS[b]	8850/3	9	8	-	-	17
Liposarcoma, well differentiated	8851/3	14	4	-	-	18
Liposarcoma, myxoid	8852/3	2	1	-	-	3
Liposarcoma, mixed-type	8855/3	1	-	-	-	1
Liposarcoma, dedifferenziated	8858/3	1	-	-	-	1
Leiomiosarcoma, NOS[b]	8890/3	15	9	4	21[c]	49
Leiomiosarcoma epithelioid	8891/3	-	-	2	1	3
Rhabdomyosarcoma, NOS[b]	8900/3	1	-	-	1	2
Rhabdomyosarcoma, embryonal	8910/3	-	-	-	1	1
Rhabdomyosarcoma, alveolar	8920/3	-	-	1	-	1
Synovial sarcoma, NOS[b]	9040/3	3	3	-	-	6
Synovial sarcoma, spindle cell type	9041/3	-	1	-	-	1
Angiosarcoma	9120/3	1	3	-	-	4
Osteosarcoma, extrascheletal	9180/3	-	-	-	1	1
Condrosarcoma, extrascheletal	9220/3	-	-	2	-	2
Malignant Schwannoma NOS[b]	9560/3	2	3			5
Subtotal		74	58	15	35	
Total		132		50		182

[a] *ICDO-3: International Classification of Diseases for Oncology, third edition*
[b] *NOS: No other specification*
[c] *13 cases with topographic site = uterus.*

is similar to the World Health Organization (WHO) classification [13]. Histological types were linked to the corresponding ICDO-3 [14] morphological codes. Sarcoma NOS (8800/3), spindle cell sarcoma (8801/3), and myxosarcoma (8840/3) were also included, whereas mesothelioma (9050/3, 9051/3, 9052/3, 9053/2) and Kaposi's sarcoma (9140/3) were excluded. Moreover, a ten years latency time, defined as the time elapsing between the beginning of residence and STS diagnosis, was required for the inclusion of the cases in the study.

For each subject the following information was collected: age, sex, year of diagnosis, site and histological type of the tumour, vital status, date of death and residence at diagnosis (that was geo-referenced using a geographic information system). Case-ascertainment procedure did not include the revision of the slides but a detailed scrutiny of the actual pathology reports and clinical records. This scrutiny permitted to exclude 17 cases incorrectly diagnosed or reported as STS. In addition, an accurate cross-linkage of the different data sets was performed in order to correctly select the true incident cases.

After the scrutiny, of the one hundred and ninety nine cases of STM diagnosed between 1990 and 2003, only 182 cases met the inclusion criteria. One case was omitted because of an uncertain diagnosis, one case because a metastatic STM, and fifteen since the latency time was less than ten years (five cases with a latency between 2 and 5 years and ten cases with a latency between 6 and 9 years).

Design of analysis

Incidence of STM was computed using age and gender specific denominators provided by the geographic information system of Verona municipality that included demographic data from 31 December 2003 and cartographic data such as road system. Data were categorized for the previously defined six exposure areas. The address of cases at time of diag-

nosis was used in order to allocate them to their corresponding residence and then exposure category.

Indirect standardization was used in order to compute standardized incidence ratios SIRs using as reference Verona municipality age and gender specific incidence rates. The hypothesis of an association between exposure levels of TSP and soft tissue sarcomas incidence was evaluated by trend-test.

RESULTS

The study includes 182 non visceral and visceral TS cases, 89 men and 93 women, aged 22 to 94: the mean age of cases at diagnosis was, respectively, 60.4 ± 16.6 and 60.6 ± 15.7. The distribution of cases by histology and sites is shown in *Table 1*. One hundred and thirty-five (72.2%) of the STS cases were non-visceral, with a predominance of male subjects, while among the fifty-five visceral cases the proportion of women was higher. The most frequent histotypes were leymiosarcomas (28.4 percent) and lyposarcomas (21.8 percent). In women 13 out of 28 cases of leyomiosarcomas were localized in uterus.

The crude incidence rates for the 182 cases are shown in *Table 2*. As expected, rates increase with age and appear higher among males in the oldest age. We also calculate the standardized incidence rates (age-standardized to Italian population of 2001) that were estimated as 6.8 per 100 000 in men and 5.6 per 100 000 in women.

Table 3 shows SIRs and their corresponding 95% confidence intervals for visceral, non visceral, and all sites STS. No data for the area with the highest TSP concentration (> 0.075 and 0.06-0.075 μg/m^3), included in the industrial area, are reported since no resident population was located there. In no case statistically significant departures between numbers of observed and expected cases by exposure category were detected as illustrated by trend-test results. Allowing for latency time did not modify the study findings (data not shown).

DISCUSSION AND CONCLUSION

In order to properly discuss the findings of the present study, some preliminary remarks on study design are required. The first point concerns the diagnosis of STS that is quite complex because of the overlapping of some morphological aspects of these tumours with other neoplasms and of the not uniformly applied criteria for diagnosis. Moreover, the STS histological classification has varied over time posing some problem in the selection of cases, especially in retrospective studies [15]. For these reasons an expert pathologic review is desirable [16]. In our study, no panel histopathological peer review of specimen was feasible, but the clinical records and the original pathological reports were thoroughly checked and reviewed. Since criteria for the selection of STS types/subtypes, inclusion or not of the visceral types, and the age at study are not uniformly applied throughout different studies, it is difficult to define the expected incidence of STS and, consequently, to comment the incidence rates observed in a specific area. According to Toro *et al.* [18] we included in our study not only the STM arising in the non-visceral sites but also the ones arising in the visceral sites. However, in order to make our data more comparable with others, we performed separated analyses according to the site of origin. In this frame, the incidence rates for the overall non-visceral and visceral STS that we find in Verona appears to be compatible with those reported in scientific literature [17, 18].

A second issue concerns exposure assessment. In the absence of an *ad hoc* DLCs monitoring system, an indirect estimation was used by modelling the spatial distribution of TSP. This procedure was performed blindly with respect to the occurrence of cases that were subsequently mapped. Due to the use of a blind procedure, no bias can be suspected, but random misclassification may not be ruled out in terms of study design.

The present study has adopted a "semi-individual" approach, as defined by Künzli and Tager [10], characterised by individual assessment of cases and by an ecological estimation of exposure based on dispersion model around a point source. A strength of the present study was that modelling was based on the estimation of TSP levels emitted from the plant, rather than on the simple notion of distance from the source, as recommended by some authors [19, 20].

Table 2 | *Number of cases and age/gender/sites specific crude incidence rates of soft tissue sarcomas (per 100 000 person years)*

Age	Non visceral sites				Visceral sites				All sites			
	Men		Women		Men		Women		Men		Women	
	N. of cases	Rate	N. of cases	Rate	N. of cases	Rate	N. of cases	Rate	N. of cases	Rate	N. of cases	Rate
20-34	7	1.9	6	1.7	0	-	3	0.8	7	1.9	9	2.5
35-64	35	4.7	23	2.9	6	0.8	18	2.3	41	5.5	41	5.2
65-74	17	10.1	14	6.2	5	3.0	8	3.5	22	13.0	22	9.7
75+	15	13.3	15	6.6	4	3.5	6	2.6	19	16.8	21	9.3
All	74	5.3	58	3.6	15	1.1	35	2.2	89	6.4	93	5.9

Table 3 | *Standardized incidence rates of soft tissue sarcomas by anatomical site, levels of exposure and gender*

	Non visceral soft tissue sarcomas											
	Men				Women				Both gender			
Levels of TSP (μg/m³)	Observed	Expected	SIR	CI 95%	Observed	Expected	SIR	CI 95%	Observed	Expected	SIR	CI 95%
0.045-0.06	1	0.1	12.9	0.3-72.1	0	0.1	-	-	1	0.1	7.8	0.2-43.4
0.03-045	2	1.9	1.1	0.1-3.8	1	1.7	0.6	0.0-3.3	3	3.6	0.8	0.2-2.4
0.015-0.03	43	40.6	1.1	0.8-1.4	31	32.9	0.9	0.6-1.3	74	73.5	1.0	0.81.3-
0-0.015	28	31.4	0.9	0.6-1.3	26	23.3	1.1	0.7-1.6	54	54.8	1.0	0.7-1.3
Total	74	74			58	58			132	132		
Trend-test		0.5967, $p = 0.4399$				0.3529, $p = 0.5525$				0.0455, $p = 0.8312$		
	Visceral soft tissue sarcomas											
	Men				Women				Both gender			
Levels of TSP (μg/m³)	Observed	Expected	SIR	CI 95%	Observed	Expected	SIR	CI 95%	Observed	Expected	SIR	CI 95%
0.045-0.06	0	0.0	-	-	0	0.0	-	-	0	0.0	-	0.0-75.70
0.03-045	1	0.4	2.7	0.1-14.8	1	1.0	1.0	0.0-5.6	2	1.36	1.47	0.18-5.30
0.015-0.03	10	8.3	1.2	0.6-2.2	20	19.6	1.0	0.6-1.6	30	27.99	1.07	0.72-1.53
0-0.015	4	6.3	0.6	0.2-1.6	14	14.3	1.0	0.5-1.6	18	20.59	0.87	0.52-1.38
Total	15	15			35	35			50	50		
Trend-test		0.8626, $p = 0.3530$				0.0039, $p = 0.9503$				0.3262, $p = 0.5679$		
	Non visceral and visceral soft tissue sarcomas											
	Men				Women				Both gender			
Levels of TSP (μg/m³)	Observed	Expected	SIR	CI 95%	Observed	Expected	SIR	CI 95%	Observed	Expected	SIR	CI 95%
0.045-0.06	1	0.1	10.5	0.3-58.6	0	0.1	0.0	0.0-45.0	1	0.2	5.6	0.1-31.5
0.03-045	3	2.3	1.3	0.3-3.9	2	2.7	0.7	0.1-2.7	5	5.0	1.0	0.3-2.4
0.015-0.03	53	48.9	1.1	0.8-1.4	51	52.6	1.0	0.7-1.3	104	101.5	1.0	0.8-1.2
0-0.015	32	37.7	0.8	0.6-1.2	40	37.7	1.1	0.8-1.4	72	75.4	1.0	0.7-1.2
Total	89	89			93	93			182	182		
Trend-test		1.1725, $p = 0.2789$				1.1847, $p = 0.6674$				0.2290, $p = 0.6323$		

TSP, total suspended particulate, daily average November 2002-March 2003; SIR, standardized incidence rate (indirect); CI,Confidence Interval;

Yet, in the absence of individual-level specific indicators of exposure, no causal inference should be directly drawn from ecological semi-individual studies [21, 22]. Rather, they should be viewed as contributing to the epidemiological framework of the areas of interest, such as polluted sites or urban districts in the neighbourhood of major industrial facilities.

In light of the aforementioned comments, the present study can be viewed as supporting the lack of association between occurrence of soft tissue sarcomas and residence in the neighbourhood of a steel foundry. In the absence of previous epidemiological investigations on this issue, and taking into account the limitations of the adopted study design, no generalized conclusion can be drawn on STS risk around foundries. Independent replications of the present study, though, appear to be warranted.

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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