Population based case control study on risk of sarcoma and dioxin emissions from incinerators (Italy)

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ABSTRACT

Background: It is not clear whether environmental doses of dioxin affect the general population. The aim of this research is to evaluate sarcoma risk in relation to the environmental pollution caused by dioxin emitted by incinerators. We examined the population which lives in the area of Province of Venice (Italy), where a population based cancer registry (Venetian Tumour Registry-RTV) has been active since 1987.

Methods: 205 cases of visceral and extravisceral sarcoma, confirmed by microscopic examination, which occurred in the period 01.01.1990 – 31.12.1996, were extracted from RTV data base. Diagnoses were revised using the actual pathology reports and/or clinical records and 186 were confirmed by the revision. For each sarcoma case three controls of same age and sex were randomly selected from the population files of Local Health Units. The residential history of each subject, cases and controls, was reconstructed, address by address, for the period 1960 – 1990. All incinerators (31) in the Province of Venice were taken into account, as was one very large incinerator outside the area but close to the boundary. The Long Term ISC model was used to assess the level of atmospheric dispersion. A specific value for exposure was calculated for each point (geo-referenced address) and for each calendar year; the exposure value for each subject is expressed as the average of specific values weighted by time. The analysis takes into account 172 cases and 405 controls, aged more than 14 years old.

Results: Risk increases in relation to both the duration and the extent of exposure and was statistically significant in the class with longest period and highest level exposure (OR= 3.30, CL 95% 1.24 – 8.76). A significant excess of risk was also observed in women (OR= 2.41, CL 95% 1.04 – 5.85); in ICD IX site, both sexes, (OR = 3.27, CL 95% 1.35 – 7.93) and in the morphological group of liposarcomas, both sexes, (OR= 4.61, CL 95%: 1.22 – 17.42).

Conclusions: Our study strongly confirms the association between dioxin and sarcoma risk.

BACKGROUND

In 1997 the International Agency for Research on Cancer (IARC) classified 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) as group I carcinogen on the basis of limited evidence on Humans, sufficient on animals and on the consideration that the Ah receptor, through which dioxin acts, is present in both humans and animals [1]. The epidemiological evidence on humans was taken from 4 cohort studies carried out on subjects occupationally exposed to high levels of dioxin and from a study on the resident population of Seveso (Milan, Italy).

In 2004 Steenland *et al*. [2] published a critical review of the literature on which the IARC evaluation had been based in 1997, and on an update; the classification of carcinogenic risk was strongly upheld by new exposure-response analyses; better checks on confounding and, by data showing a significant overall cancer excess.

Recent studies have looked at the effects of low levels of environmental exposure, for example to the dioxin produced by incinerators. This exposure is usually expressed in terms of I-TEQ (International Toxic Equivalency Factor) insofar as the so-called dioxin like substances, e.g. polychlorinated dibenzo-para-dioxins (PCDDs), polybenzofurans (PBFs) and dioxinlike polychlorinated biphenyls (PCBs) whose toxicity should be compared with that of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the so-called “Seveso dioxin” [3].

We have carried out a registry based case-control study on the population resident in three former Local Health Units (LHUs) in the Province of Venice (Italy) in order to evaluate the relationship between the risk of sarcoma and environmental exposure to dioxin emitted by the incinerators that had been operating in the area. The population studied was composed of 422,924 local residents, about half the total population of the Province. Since 1987 a population based cancer registry, the Venetian Tumour Registry (RTV) which covers in all about 2,000,000 of residents, has been covering this area too.

METHODS

Selection of cases and controls

All cases of malignant sarcoma, confirmed by histological examination, in all age groups, in all sites, which occurred in the period between 01.01.1990 – 31.12.1996 were extracted from the RTV data base. The ICD–O II morphologies were chosen on the basis of criteria adopted by another case-control study that evaluated the presence of an analogous causal relation [4].

- M 880 – 892: NOS sarcoma, fibrosarcoma, myxosarcoma, liposarcoma, myosarcoma;
- M 899: mixed mesenchymal sarcoma,
- M 904: synovial sarcoma
- M 912-913, M915 – 916: blood vessel sarcoma
- M 917: lymphatic vessel sarcoma
- M 954 – 957: nerve sheath sarcoma
- M 958: alveolar sarcoma

Mesoteliomas, Kaposi sarcomas, mixed forms and sarcomas with C 40 - 41 (bone) topography were excluded.

Diagnoses were revised using the actual pathology reports and/or clinical records, immunohistochemical examinations were almost always available.

205 cases met the criteria for inclusion and were resident at the time of diagnosis in one of the Municipalities of the 3 former LHUs of the Province of Venice: 186 cases (90.7%) were confirmed by the revision.

We used controls drawn from the general population by extracting names from the population files of the 3 LHUs studied, after having back-dated this information on the population to 1990 so as to include subjects who had subsequently died, or moved their place of residence, after that date.

For each case, three control subjects were chosen at random among those of the same sex and age at the time of diagnosis. However, subjects who were already in the RTV data base with a diagnosis of sarcoma or Non-Hodgkin’s lymphoma were replaced, as both these neoplasias have been associated with exposure to dioxins.

Reconstruction of Residential History

The residential history of each subject (186 cases and 558 controls) was reconstructed address by address for the period since 1960. Information was gathered from the Population Registries of each of the Municipalities where the subject had lived during the 30 year period studied. Each address, (total 1,823) in the Province, was then geo-referenced, using the Roma 40 System of reference and Gauss Boaga representations. Only five addresses were inexistent as they are protected places of residence.

Exposure

The exposure to dioxin like substances was assessed exclusively for the addresses of residents in the Municipalities of the Province of Venice: because information regarding the presence and activities of incinerators was only available for this area.

All incinerators active in the Province of Venice were taken into account as was one very large incinerator, very close to the boundary, in the neighbouring Province of Padua.

Thirty-three incinerators were studied: 7 industrial waste incinerators, 3 electricity power station, 10 solid urban waste incinerators (RSU), 12 hospital waste incinerators (RO), 1 refinery.

The amounts of emissions were calculated through a historical reconstruction of the technology adopted by each plant and the quantity and quality of the waste / refuse treated. This information was taken from technical and administrative documentation held in the archives of the Province of Venice.

The Long Term ISC model, developed by US EPA, was used to assess the level of atmospheric dispersion of the polluting substances; the model takes wind speed and direction and the degree of atmospheric stability which causes fog to form [5].

A specific value for exposure was calculated for each point (geo-referenced address) and for each calendar year. This exposure value was expressed in fentograms/m^3 of I-TEQ (PCDD, PCDF); the calculation was done for each incinerator within a 50 kilometres radius of each point (address). The overall value for each address in a given year is the total of the values calculated for each incinerator active during that year. The exposure value for each subject is expressed as the average of specific values weighted by time, i.e. by the number of days the subject lived at that specific address.

The amount of emission varies greatly from one incinerator to another and, also, over time (Table 1). Figure 1 shows a graphic of the amount of the emissions overtime; the value of each year was obtained by adding the emissions of all the incinerators active in that year. The maximum was reached in the period 1972 – 1986 after which emissions returned to their former level.

Population on analysis

The following subjects were excluded from the population studied:

- 3 childhood cases, born after 1986 when the exposure studied had ceased;
- 2 cases, correlated with recognised risk factors: one radio-induced case and one associated with von Rechlinghausen's disease [6]
- 9 cases, not continuously residents in the Province, or moved there after 1969. Until 1969 exposure levels were low and we felt that subjects living outside the Province of Venice between 1960 and 1969 would not have been exposed to dioxin emissions from incinerators because the first industrial incinerators in Italy were in Porto Marghera (mainland Venice) and in 1960 only two were active; furthermore the Veneto Region was the first Region in Italy to construct incinerators for solid urban waste (1962 on);
- 17 controls because the Municipal Population Registers showed that either they were no longer resident or that they had died, by 1990;
- 42 controls, paired with the 14 cases excluded from the study;
- 59 controls with malignant tumours, all sites , registered in the RTV data base, because dioxins are considered to be carcinogens for all types of cancer: only cases of cutaneous epithelium were accepted;
- 35 controls, not continuously resident in the Province or, moved there after 1969.

Some subjects were excluded for more than one reason; in this case only the first reason given in the list above counted.

The population on analysis was made up of: 172 cases (92.5%) and 405 controls (72.6%).

Table 2 shows the number of subjects extracted, sub-divided by sex, status, age and reason for exclusion.

Analyses were done on the total population, divided into three classes of average exposure and two classes of length of exposure and in the following sub-groups: sex; ICD IX site and morphological group. These sub-groups were only analysed for level of exposure because the time-period variable was not significant. Table 3 shows the distribution of cases in the sub-groups analysed.

We used conditioned logical regression to calculate Odds Ratios (ORs) values and 95% Confidence Limits [7].

RESULTS AND DISCUSSION

In the population analysed, cases and controls taken together, the median exposure value was 4.25 fentogramms/m^3, (minimum 0.23 fgr/m^3, maximum 14.57 fgr/m^3); the median value of length of exposure was 32.74 years (minimum 18.41, maximum 36.93).

Table 4 shows the distribution of cases and controls in relation to the three levels of average exposure and two classes of duration of exposure, with the corresponding Odds Ratio (OR) values and confidence limits (CL 95%). Risk increases in relation to both the duration and the extent of exposure and is statistically significant in the class with longest period and highest level of exposure (OR = 3.30, CL 95% 1.24 – 8.76).

In both sexes, risk increases in relation to the level of exposure and among women most exposed the risk excess (OR = 2.41, CL 95% 1.04 – 5.85) and the test for trend were significant (Table 5).

Table 6 shows analysis for ICD IX site. In the most exposed cases, both sexes, with ICD IX 171 site, there was a significant risk excess (OR= 3.27, CI 95% 1.35 – 7.93), above all in women (OR = 4.39, CL 1.14 – 16.93). However the increasing level of risk was also marked among men. Risk increases even for visceral sites, while for sarcomas in retroperitoneal (ICD IX 158) and cutaneous (ICD IX 173) sites there was no evidence of risk.

Table 7 shows the results of analysis by morphological group: in liposarcomas the risk excess is statistically significant (OR = 4.61, CI 1.22 – 17.42, trend test significant) for both sexes taken together.

The low number of subjects made it impossible to analyse for sex and for the three levels of exposure; if one considers only two levels (less than 6 fgr/m^3 equal or more than 6 fgr/m^3), the OR value for men (15 cases, 32 controls) was 9.97 (LC 95%:1.12-89.07) and for women (22 cases, 51 controls) OR = 3.33 (LC 0.75 – 14.69).

Increasing risk was also found for fibrosarcomas and, though to a lesser extent, miosarcomas; there was no evidence of risk of nerve tissue sarcoma.

The results of our research show, clearly, that there is a significant increase in the risk of sarcoma, correlated both with the level, and the length, of environmental exposure to dioxin-like substances. Among women the excess can be seen both overall and, in particular, for the ICD IX 171 site (soft tissue sarcomas); in men the excess of risk is particularly clear in the morphological group of liposarcomas.

The first step in our analysis was to calculate the risk among the permanent resident population of the area between 1960 and 1990 or, for younger subjects, resident from birth: 168 cases and 384 controls with a median exposure value of 4.22 fgr/m^3 and a median duration of 32.84 years. Analysis by quartiles of the population, with cases and controls taken together, revealed an OR value of 1.86, with LC at 95%: 1.11 – 3.13 in the most exposed quartile. This OR value is almost the same as that related to the highest level of exposure calculated on a population of 172 cases and 405 controls, which includes the 25 subjects who moved to live in the Province of Venice after 1969: OR=1.91, LC 95% 1.14 – 3.19.

Consequently, further analysis was carried out on this population of 172 cases and 405 controls.

A few observations should be made here regarding certain methodological aspects.

As regards the selection and checking of cases, we feel that they have been correctly and completely identified, as they are incident cases taken from an internationally recognised tumour registry (RTV) that has been active for many years [8, 9].

By consulting the actual pathology reports we were able to eliminate both mixed forms (carcinosarcomas) and “possible” diagnoses, and also to check that, for most cases, there was more than one report available as well as immunochemistry tests; this documentation also allowed us to eliminate cases associated with known risk factors. We used the LHU population files in order to obtain our control population. We found a few errors regarding Municipality of residence and vital status in some of the records for the period. However this reconstruction of each subject’s residential history on the basis of Local Municipal archives allowed us to retrospectively eliminate those subjects who were not resident in the areas studied, or who had died, before 1990. About 10% of the controls were excluded from the study because they were affected by malignant cancer (all sites) registered in RTV data base; 6% of the controls were excluded on grounds of residency, which is not very different from the 4.8% of the cases excluded for the same reason. The final ratio of cases to controls was 2 : 3 for men and 2 : 4 for women.

The most complex methodological question concerns how dioxin exposure was calculated.

The long-term type ISC3 dispersion model, developed by the US Environmental Protection Agency (US EPA), starts by looking at analytical data on the activity of the plants.

The data relating to both industrial production and industrial waste disposal plants should be considered very reliable in that they have been taken from both the detailed documentation held in the Archives of the Province of Venice and from documents accepted as evidence in the “Petrochemicals Trial” [10, 11].

Three RSU were studied using documents and analyses produced during investigations which resulted in the closure of these RSUs. Information on the other RSU’s is less detailed and complete, however, it was always possible to reconstruct a reliable model of how the plant functioned.

It was more difficult to obtain documents relating to hospital waste incinerators, but there was enough information to identify the period when the plant was active and the type of incinerator used with acceptable accuracy, given that these incinerators used standard technology The quantity of waste disposed of was calculated on the basis of parameters (number of beds; their level of occupation) given in documents, gathered by the Veneto Region when it decided to close all these incinerators.

The ISC3 dispersion model also requires the following meteorological variables: wind direction, speed and frequency; classes of atmospheric stability and vertical remixing. The only source of this information for the period required were weather records from Venice Airport. These were used to calculate the emissions over the whole area and this could mean that estimates for the more distant incinerators are less accurate. However, we feel that this method does offer a fairly good representation of exposure for various reasons.

Because we had observed that addresses in the Riviera del Brenta Local Health Unit Area had higher exposure value, we did a cluster analysis using two models (Spatial Scan Statistic using Satscan software) [12]. In this analysis we considered, for every subject, only the geographical location of the address where he/she was resident in the peak period for emissions (1972-1986). When a subject had lived at more than one address in that period then the address, which they had lived for the longest period, was taken into account (prevalent address). Length of period of residency was greater than 10 years out of 15 for 86% of subjects and greater than 13 out of 15 years for 67%.

The first model (Bernoulli's Model) used the entire population involved in the study, both cases and controls, and identified a spatial cluster of 19 cases and 9 controls with prevalent addresses in the Municipalities of Stra, Vigonovo, Fiesso d'Artico and Dolo. The expected number of cases for that area would be 8.35 and the RR (Relative Risk) was equal to 2.43, statistically significant (p=0.048) (Figure 2).

The second model (Poisson Model) only considered the cases, and identified a cluster for the Municipalities of Stra, Vigonovo and Fiesso d'Artico, with a statistically significant Relative Risk value that was very close to that of the other model: cases observed=17, cases expected =7.91, RR=2.27, p=0.033.

Cluster analysis identifies a risk excess with a spatial distribution that is coherent with that calculated as average exposure, weighted for time, and with the prevailing wind direction with respect to the location of the incinerators. Furthermore, the excess risk given by cluster analysis is largely the same as the SIR (Standard Incidence Ratio) calculated by the RTV for all incident cases of sarcoma in the period 1990 – 1996. The SIR value for males, for all sarcomas (visceral and extra-visceral) was 1.6 (95% CL 1.0 – 2.3) and for ICD IX 171 site : SIR = 1.82 (95% CL 1.13-2.69); for women the SIR for all sarcomas was: 1.7 (95% CL 1.1 – 2.4) and for ICD IX 171 site : SIR 2.28 (95% CL 1.44 – 3.30) [13].

There were no subjects in this population who had not been exposed: 25% had an average exposure level below 3.79 fgr/m^3 and 50% had exposure levels that ranged between 3.80 and 4.91 fgr/m^3.

The fact that exposure levels are quite high throughout the whole Province, to the extent that there were no subjects with low or very low exposure, is explained by the high number of incinerators active in the area. Indeed, 40% of the study population had lived at an address that was less than two kilometres from an incinerator; the percentage rose to 88% if one considered those who had lived within a 5 kilometres radius of an incinerator.

In 2003 a comparison was made between the modelled and monitored concentrations of the three polluting substances (SO2, PTS, Nox); the agreement between the two different values for SO2 was more than satisfactory while for PTS and Nox which, unlike SO2, are not mainly of industrial origin, there was a larger difference [14]. However, because there are no measurements of dioxin levels available for the period studied, we cannot check our estimates against historical samplings .

We evaluated other hypotheses of risk factors as alternatives, or concurrent to the environmental pollution considered here: factors such as eating habits, and occupational exposure.

The three LHUS cover a relatively small population (423,000 residents) and there is no reason to suppose that the eating habits of the cases are very much different from those of the controls, or that those of the people living on the Riviera del Brenta (inland) should be so very different from those of the Venetian lagoon dwellers. Furthermore, a recent study carried out by the Veneto Region to monitor the level of dioxins and PCBs in foodstuffs (fish, meat, eggs milk) suggested that the highest levels of these substances are found in shellfish, which are probably eaten more often in the lagoons area [15].

We have no information about social status and only partial knowledge regarding occupation, however, we feel that it is unlikely that exposure at work will have had much influence for the following reasons.

As regards cases between 35 – 69 years, private sector workers, still active in 1974, the names of the firms they worked for in various industrial sectors are recorded in the electronic database of the INPS (Italian National Institute for Social Security) [16]. Only 35 subjects were found in this list, none of whom would appear to have worked in areas of production where there was a risk of exposure related to sarcoma. To our knowledge, there were no industries where there would have been risk of exposure to dioxins operating in the area at the time.

As regards older subjects, it could be argued that the period of latency of any exposure to carcinogens at work (except for asbestos and ionising radiation) would have already passed, while that related to environmental pollution, for these subjects, only began when they were already at the age of retirement. The period of latency since the first exposure 1972-1986 is however consistent for younger subjects (15 years) too, those born between 1975 and 1981.

Lastly, the higher risk observed in women was unlikely to be due to occupational exposure, rather it was primarily attributable to environmental exposure, given that women were less mobile in the past and would have rarely been subject to risk of exposure to the pollutants studied while at work.

A recent review of the literature on epidemiological studies of the effect on health of exposure to emissions from waste incinerators, has reported that a significant association between exposure and cancer was made in two thirds of the studies published by 2003 [17]; the strongest evidence of an association is in lung cancers, cancer of the larynx and non Hodgkin Lymphoma. The emissions from incinerators contain various substances classed as certain or suspected carcinogenic: metals, heavy metals, Polyaromatic Hydrocarbons (PAHs), polycyclic aromatics (PCA), dioxin (Polychlorinated debenzo-oara-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs).

Exposure to dioxin has been associated with an increased risk of sarcoma [18, 19, 20, 21, 22, 23], but the results of the study are not yet conclusive. The most recent study [24], carried out in Finland, examined 110 cases of soft tissues sarcoma and 227 hospital controls paired for age and district/place of residence, exposure to dioxin was measured using the concentrations found in sub-cutaneous fat samples taken from tissue removed during operations. Risk does not increase with exposure; rather, the lowest level shows the highest risk in all analyses.

However it should be observed that for 148 of cases dioxin values were available but full analysis was, eventually, carried out on only 110 cases (74%) because there was a lack of controls to match with the cases. No data concerning age, sex, and dioxin values were given for the 38 subjects eliminated from the study. The study does not take either visceral tumours into account or those with "bone" sites, but 4 cases with Ewing's Sarcoma morphology and three with chondrosarcoma, given the ICD-O rules of classification should have been attributed to "bone" topography [25].

So far very few studies have analysed the relationship between risk of sarcoma and emissions from incinerators. In 2000, Viel *et al* [26] identified a cluster of sarcomas and non-Hodgkin lymphomas in a population living near an urban waste incinerator, with high levels of emissions, at Besançon, France. Later studies have confirmed the result for non-HD lymphomas [27], but not for sarcomas [28]. Excess risk for non-HD lymphomas was only present in the area with the highest estimated concentrations of dioxin.

Comba *et al*. [4] reported a significant increase in the risk of sarcoma associated with living within a two Kilometres radius of an incinerator burning industrial waste. The cluster is remarkable for the net prevalence of women among the cases: given that these women would not have been exposed to risk for occupational reasons, there can be no other explanation apart from the distance they lived from the incinerator and excess risk does not extend beyond the 2 kilometre radius.

In order to define the level of exposure, the two studies done in France, on clusters of non-Hodgkin lymphomas and sarcomas, used a Gaussian type dispersion model which highlighted wind direction when identifying areas with different levels of pollution and gave a geographical representation of pollution which was possible because they were only looking at one source of emissions. The same authors also did a further study in order to validate their method, using soil samples. On flat lands they discovered a significant association between their estimated dioxin concentrations and the log-transformed measured dioxin soil concentrations, while in the more topographically complex areas their model tended to over-estimate concentrations [29].

We used an analogous dispersion model, but we cannot give a geographical representation of the estimated dioxin soil concentrations because we were dealing with a large number of points of emission (33 incinerators) and, above all, because we calculated the values of exposition for each address of each subject over a period of 30 years. From the topographical point of view the entire Province is completely flat, so our estimates probably do give a good estimate of dioxin exposure.

CONCLUSIONS

We feel that the results of our study strongly confirm the association between dioxin and sarcomas and we would like to observe that, given the fact so many incinerators were functioning in one period in the examined area - which was not known when the study began - the hypothesis that the general population must have been exposed to, at least, low levels of dioxin should be checked.

List of abbreviations

RTV: Venetian Tumour Registry

IARC: International Agency for Research on Cancer

TCDD: tetrachlorodibenzo-p-dioxin

I-TEQ: International Toxic Equivalency Factor

PCDDs: polychlorinated dibenzo-para-dioxins

PBFs: polybenzofurans

PCBs: dioxinlike polychlorinated biphenyls

OR: Odd Ratio

CL: Confidential Limit

SIR: Standard Incidence Ratio

LHU: Local Health Unit

RSU: solid urban waste incinerators

RO: hospital waste incinerators

PAHs: Polyaromatic Hydrocarbons

PCA: polycyclic aromatics

PCDFs: polychlorinated dibenzofurans

ICD-O: International Classification of Diseases for Oncology

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PZ is the principal investigator of this study. As such she participated in the design, planning, data analysis and writing of the present paper.

PR contributed equally to this work.

EB created the SAS archive of the residential history of the subjects and performed the geo-referencing of addresses.

SG performed the statistical analysis.

AC, MG and FC gathered analytical information on the incinerators and estimated the values of exposure at each, geo-referenced point.

ARF contributed to the revision of the diagnoses.

All authors read and approved the final manuscript

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Figure 1 - Emissions trend: summary for single year of the emission values of incinerators (I-TEQ gr/sec)

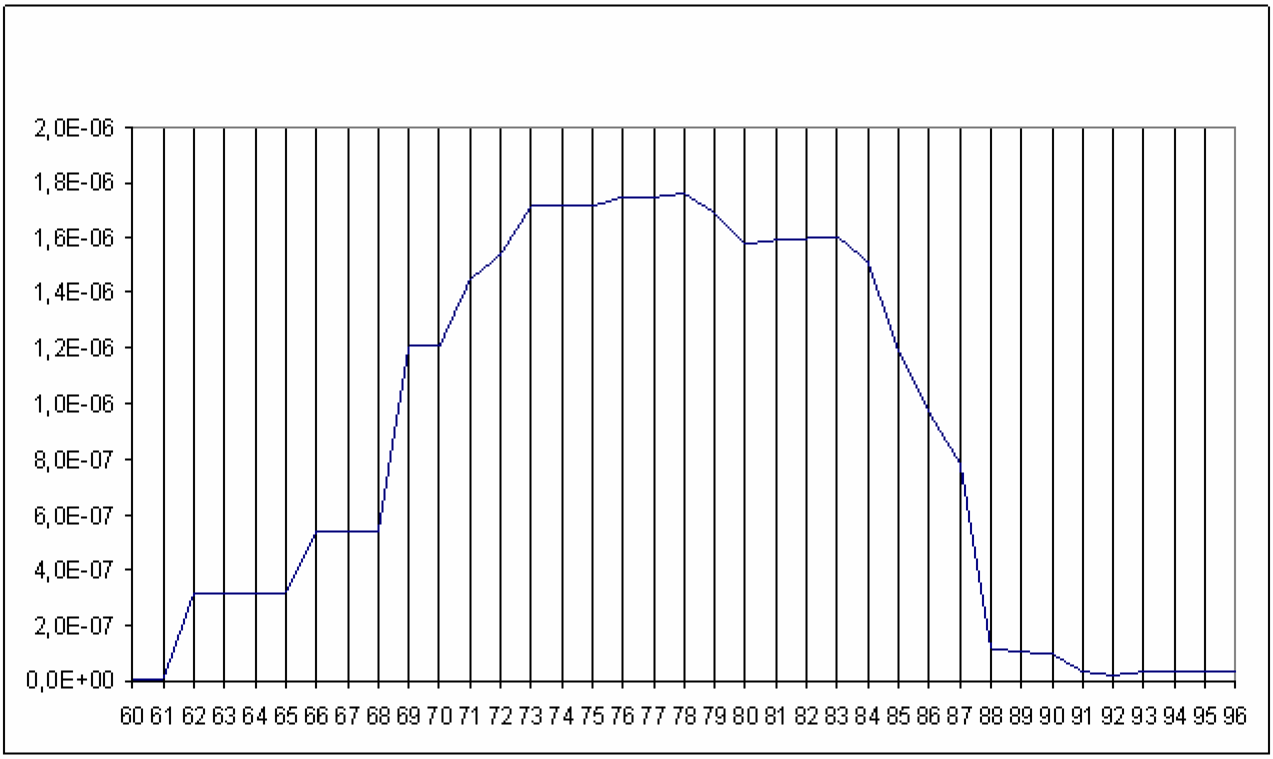

Figure 2 – Location of incinerators in the Province of Venice

The small figure shows the cluster of sarcoma cases.

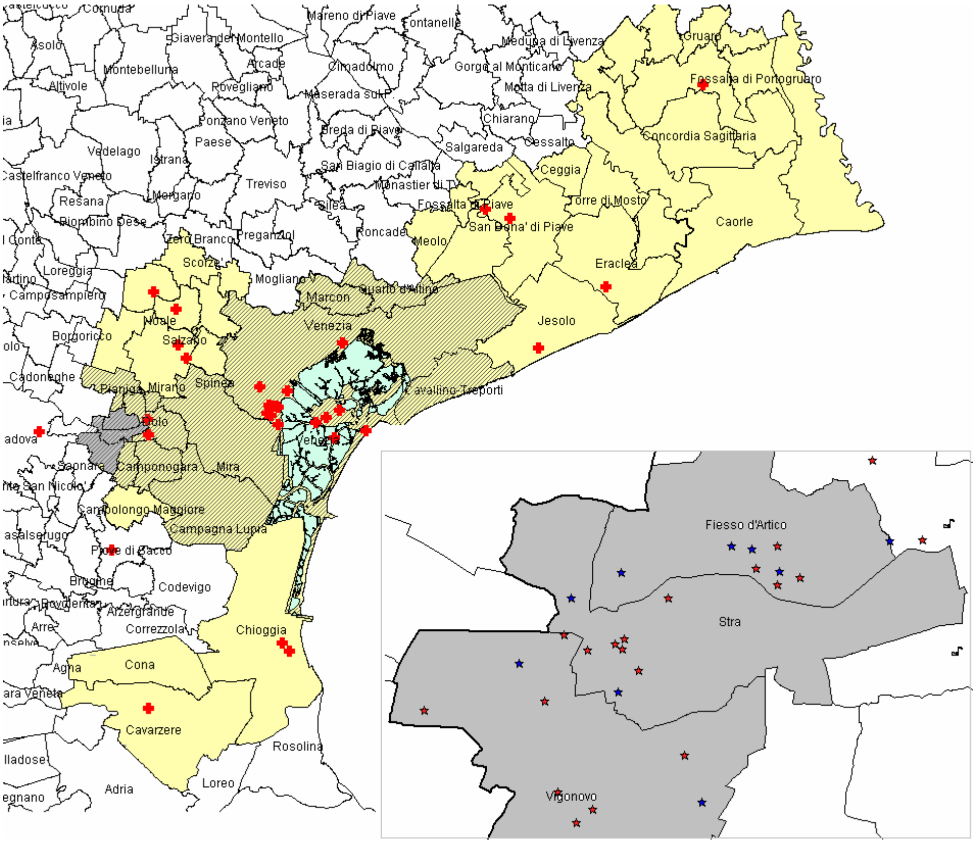

Table 1 – List of incinerators

Typology	Municipality	Period of working examined	Height of chimney	Chimney concentration (I-TEQ gr/s)
Municipal solid waste	Padua	1962-1968	60 mt	3.11*E-7
		1969-1987	60 mt	6.44*E-7
		1988-1996	60 mt	1.56*E-8
Municipal solid waste	Venice	1969-1984	40 mt	3.33*E-7
Municipal solid waste	Mirano – province of Venice	1972-1975	26 mt	8.89*E-8
		1976-1983	26 mt	2.39*E-7
		1984-1986	26 mt	1.50*E-7
Municipal solid waste	Jesolo - province of Venice	1966-1975	20 mt	2.22*E-7
Municipal solid waste	Chioggia - province of Venice	1971-1985	30 mt	2.20*E-7
Municipal solid waste	San Donà - province of Venice	1973-1979	15 mt	1.78*E-7
Municipal solid waste	Dolo - province of Venice	1976-1978	8 mt	8.90*E-8
Municipal solid waste	Eraclea - province of Venice	1980-1998	13 mt	6.48*E-8
Municipal solid waste	Salzano - province of Venice	1971-1977	15 mt	2.20*E-8
Municipal solid waste	Venice Airport	1982-1988	9 mt	1.11*E-8
Hospital waste	Dolo - province of Venice	1978-1986	8 mt	4.33*E-8
Hospital waste	Piove di Sacco - province of Padua	1978-1987	8 mt	2.70*E-8
Hospital waste	Cavarzere - province of Venice	1979-1986	8 mt	1.53*E-8
Hospital waste	Venice	1981-1987	8 mt	1.10*E-8
Hospital waste	Noale - province of Venice	1979-1986	8 mt	6.76*E-9
Hospital waste	Chioggia - province of Venice	1980-1987	8 mt	3.80*E-9
Hospital waste	San Donà - province of Venice	1976-1986	8 mt	3.21*E-9
Hospital waste	Venice	1968-1986	8 mt	6.30*E-11
Hospital waste	Venice	1975-1986	8 mt	4.90*E-11
Hospital waste	Mirano - province of Venice	1970-1986	8 mt	4.21*E-11
Hospital waste	Portogruaro - province of Venice	1978-1987	8 mt	3.40*E-11
Hospital waste	Venice	1969-1986	8 mt	3.00*E-11
Electricity power station Fusina	Venice	1963-1968	150 mt	3.17*E-9
		1969-1975	150 mt	6.33*E-9
		1990-1996	150 mt	1.11*E-8
Thermal power station Marghera	Venice	1960-1989	100 mt	3.38*E-9
		1990-1996	100 mt	3.17*E-9
Thermal power station Alumix	Venice	1960-1984	60 mt	8.33*E-10
Industrial waste SG31	Venice	1983-1996	70 mt	1.39*E-9
Industrial waste Peabody	Venice	1984-1996	43 mt	1.11*E-9
Industrial waste E79	Venice	1993-1996	50 mt	3.06*E-10
Aluminium – 3 chimneys	Venice	1960-1969	12.5 mt	9.96*E-12
		1970-1979		3.80*E-11
		1980-1989		4.09*E-11
		1990-1999		4.51*E-11
Industrial waste CS28	Venice	1972-1974	36 mt	1.67*E-10
		1975-1996	36 mt	3.33*E-11
Refinery	Venice	1960-1965	60 mt	2.73*E-10
		1966-1989	60 mt	8.43*E-10
		1990-1996	60 mt	1.05*E-9

Table 2 – Recruitment levels among cases and controls by sex and age, and reasons for exclusion

Males

AGE	CASES					CONTROLS					
	Extracted from RTV	Recruited	Excluded due to			Extracted from population files	Recruited	Excluded due to			
			Born after 1986	Diagnosis	Residence			Population files errors	Matched with excluded cases	Malignant tumour	Residence
0 – 14	2	-	2	-	-	6	-	-	6	-	-
15 – 24	5	4	-	-	1	15	10	2	3	-	-
25 – 34	2	1	-	1	-	6	3	-	3	-	-
35 – 44	10	9	-	-	1	30	20	1	3	1	5
45 – 54	14	13	-	1	-	42	33	1	3	1	4
55 – 64	18	18	-	-	-	54	46	1	-	3	4
65 – 74	20	19	-	-	1	60	39	1	3	12	5
75 – 84	20	19	-	-	1	60	38	6	3	12	1
85+	4	4	-	-	-	12	8	1	-	3	-
Total	95 100%	87 91.6%	2 2.1%	2 2.1%	4 4.2%	285 100%	197 69.1%	13 4.6%	24 8.4%	32 11.2%	19 6.7%

Females

AGE	CASES					CONTROLS					
	Extracted from RTV	Recruited	Excluded due to			Extracted from population files	Recruited	Excluded due to			
			Born after 1986	Diagnosis	Residence			Population files errors	Matched with excluded cases	Malignant tumour	Residence
0 – 14	1	-	1	-	-	3	-	-	3	-	-
15 – 24	2	2	-	-	-	6	6	-	-	-	-
25 – 34	3	2	-	-	1	9	6	-	3	-	-
35 – 44	7	7	-	-	-	21	13	1	-	1	6
45 – 54	11	11	-	-	-	33	29	-	-	-	4
55 – 64	17	15	-	-	2	51	40	-	6	3	2
65 – 74	19	19	-	-	-	57	46	1	-	10	-
75 – 84	22	20	-	-	2	66	47	-	6	11	2
85+	9	9	-	-	-	27	21	2	-	2	2
Total	91 100%	85 93.4%	1 1.1%	-	5 5.5%	273 100%	208 76.2%	4 1.5%	18 6.6%	27 10.0%	16 5.9%

Table 3 – Sex distribution of sarcoma cases by ICD IX site and morphology group

Males	Sarcoma NOS	Fibrosarcoma	Liposarcoma	Myosarcoma	Other morphologies*	Nerve Sheath	Total	
ICD IX 171	4	6	9	11	9	4	43	49.9%
ICD IX 173	-	9	-	-	-	-	9	10.3%
ICD IX 158	2	1	3	3	1	-	10	11.5%
All other sites	3	2	3	13	2	2	25	28.8%
Total	9 (10.3%)	18 (20.7%)	15 (17.2%)	27 (31.0%)	12 (13.8%)	6 (7.0%)	87	(100.0%)
Females								
ICD IX 171	2	7	13	11	-	5	38	44.7%
ICD IX 173	-	8	-	-	-	-	8	9.5%
ICD IX 158	1	-	7	3	-	-	11	12.9%
All other sites	4	1	2	18	1	2	28	32.9%
Total	7 (8.2%)	16 (18.8%)	22 (25.9%)	32 (37.7%)	1 (1.2%)	7 (8.2%)	85	(100.0%)

*Other morphologies Males: 8 cases of Synovial sarcoma (M904) and 4 cases of blood vessel sarcoma (M912)

Other morphologies Females: 1 case of blood vessel sarcoma (M912)

Table 4 – ORs of sarcoma (both sex) according to length and levels of exposure.

Cases/controls: 172/405

	Average exposure fgr/m^3	Ca/Co	OR	CL 95%
Length of exposure <32 y				
	<4	10/41	1.00	
	4 – 6	41/100	1.67	0.76 – 3.68
	≥6	14/26	2.57	0.95 – 6.92
Length of exposure ≥32 y				
	<4	45/120	1.61	0.71 – 3.63
	4 – 6	42/92	1.91	0.84 – 4.34
	≥6	20/26	3.30	1.24 – 8.76
	Test for trend < 32 years	1.47		0.89 - 2.41
	Test for trend > 32 years	1.35		0.97 - 1.87

Table 5 - ORs of sarcoma (all sites), according by sex and levels of exposure.

	Males			Females		
Average of exposure fgr/m^3	Ca/Co (87/197)	OR	CL 95%	Ca/Co (85/208)	OR	CL 95%
<4	31/83	1.00		24/78	1.00	
4 – 6	39/88	1.10	0.63 – 1.96	44/104	1.47	
≥6	17/26	1.86	0.87 – 3.95	17/26	2.41	1.04 – 5.85
Test for trend	1.30		0.91-1.88	1.54		1.02 - 2.31

Table 6 – ORs of sarcoma according to ICD IX site and levels of exposure

ICD IX 171	Average exposure fgr/m^3	Ca/Co	OR	LC 95%
Both sex (Ca/Co: 81/190)				
	<4	25/80	1.00	
	4 - 6	39/93	1.35	0.73 – 2.48
	≥6	17/17	3.27	1.35 – 7.93
	Test for trend		1.69	(1.11 – 2.58)
Females (Ca/Co:38/93)				
	<4	12/40	1.00	
	4 - 6	17/46	1.27	0.53 – 3.05
	≥6	9/7	4.39	1.14 – 16.93
	Test for trend		1.83	0.98-3.42
Males (Ca/Co: 43/97)				
	<4	13/40	1.00	
	4 - 6	22/47	1.42	0.61 – 3.32
	≥6	8/10	2.62	0.80 - 8.62
	Test for trend		1.58	0.89 – 2.81
ICD IX 173				
Both sex (Ca/Co: 17/43)				
	<4	5/12	1.00	
	4 - 6	10/20	1.20	0.31 – 4.71
	≥6	2/11	0.34	0.03 – 3.43
	Test for trend		0.71	0.28 – 1.81
ICD IX 158				
Both sex (Ca/Co: 21/49)				
	<4	6/14	1.00	
	4 - 6	12/27	1.06	0.33 – 3.43
	≥6	3/8	0.80	0.14 – 4.45
	Test for trend		0.93	0.42 – 2.06
Visceral sarcoma				
Both sex (Ca/Co: 53/123)				
	<4	19/55	1.00	
	4 - 6	22/52	1.24	
	≥6	12/16	2.45	0.96 – 6.28
	Test for trend		1.50	0.95 – 2.37

Table 7 – ORs of sarcoma according to morphological group and exposure levels (both sex)

Morphologic group	Average exposure fgr/m^3	Ca/Co	OR	CL95%
Sarcoma NOS				
Both sex (Ca/Co: 16/36)				
	<4	6/13	1.00	
	4 – 6	6/13	0.92	0.14 – 6.28
	≥6	4/10	0.88	0.16 – 4.82
	Test for trend		0.94	0.41 – 2.17
Fibrosarcoma				
Both sex (Ca/Co: 34/79)				
	<4	6/29	1.00	
	4 – 6	21/39	2.55	0.90 – 7.25
	≥6	7/11	3.04	0.79 – 11 .78
	Test for trend		1.85	0.97 – 3.55
Liposarcoma				
Both sex (Ca/Co: 37/83)				
	<4	11/34	1.00	
	4 – 6	14/40	0.86	0.27 – 2.72
	≥6	12/9	4.61	1.22 – 17.42
	Test for trend		2.03	1.04 – 3.96
Myosarcoma				
Both sex (Ca/Co: 59/150)				
	<4	20/61	1.00	
	4 – 6	31/72	1.30	0.67 – 2.53
	≥6	8/17	1.45	0.54 – 3.92
	Test for trend		1.23	0.77 – 1.96
Nerve Sheath Tumours				
Both sex (Ca/Co: 13/29)				
	<4	6/12	1.00	
	4 – 6	6/14	0.92	0.23 – 3.67
	≥6	1/3	0.59	0.05 – 7.39
	Test for trend		0.83	0.29 – 2.36
All other morphologies				
Both sex (Ca/Co: 13/28)				
	<4	6/12	1.00	
	4 – 6	5/14	0.70	0.18 – 2.71
	≥6	2/2	1.61	0.21 – 12.34
	Test for trend		1.04	0.41 – 2.62