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Ecological Study on Digestive and Bladder Cancer in Relation to the Level of Trihalomethanes in Drinking Water

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ABSTRACT: Complex mixtures of disinfection by-products are formed in drinking waters when chlorine is used as disinfectant, among which are found trihalomethanes. Trihalomethanes are very stable in the natural environment and are moderately lipophilic. Thus they accumulate in the human organism, which may be related to a greater risk of certain cancers.The objective of this study is to investigate the association between trihalomethanes exposure (e.g. total trihalomethane concentration, TTHM; occurring as chlorination of drinking water) and bladder and certain digestive cancers. Data were collected on different districts inside a Mediterranean city (Valencia, Spain). Samples were analyzed via head-space and electron capture detector to determine TTHM concentrations. The relative influence of different factors has been evaluated. Our results suggest a possible association between bladder cancer in women and trihalomethanes' exposure at levels below the European Community legal limit; that, at least, advices that such studies deserves more attention.

Key words: Bladder, Digestive, Cancer, Disinfection, Water, Trihalomethanes

INTRODUCTION

Disinfectants in drinking water lead to highly reactive molecules which, through an interaction with organic material, generate a series of compounds known as Disinfection By-Products (DBPs). Of these disinfectants, the most used is chlorine. Chlorine may produce trihalomethanes (THMs), the most common DBPs (Kampioti and Stephanou, 2002; Nissinen *et al*.,, 2002; Richardson *et al*., 2003; Yoon *et al*., 2003; Hassani et al., 2010). The level of THMs (specifically the sum of trichloromethane, dichlorobromomethane, dibromochlorometane and tribromomethane, the so-called total trihalomethanes, abbreviated as TTHM) in drinking water is officially regulated. According to Directive 98/83/EC, a maximum TTHM concentration of 150 (but 100 in 2009) µg/Lin drinking water is permissible.

It has been demonstrated that the cities of the Mediterranean basin have high levels of TTHM, which cause specific problems in these areas (Kampioti and Stephanou, 2002; Villanueva *et al*., 2001). Furthermore, these cities have a special relevance as they are supplied by surface sources to obtain water, whit present the largest amount of organic material (Nissinen *et al*., 2002). The city of Valencia in Spain fulfils both circumstances. Therefore the study on TTHM in its waters is especially appropriate. THMs are very stable in the natural environment and are moderately lipophilic. Thus they accumulate in the human organism (Calderón 2000), which may be related to a greater risk of certain cancers. In the last years several articles on THMs and its relation on cancer have been published without any absolute results. Epidemiological studies, backed by previous ecological studies, have suggested a possible association between exposure to THMs and an increased risk of cancer. This association is supported by experimental studies on the carcinogenesis of some of these compounds (Villanueva *et al*., 2001). Although the genotoxicity of these compounds has been approached in laboratories, *in vitro* and *in vivo*, its

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mechanism of action remains unknown. Very few works have studied genotoxicity markers in humans (Villanueva *et al*., 2007). Bladder cancer is more highly associated with THMs exposure (Villanueva *et al*., 2001; Villanueva *et al*., 2004; Villanueva *et al*., 2007); ingestion is apparently the main exposure route (Villanueva *et al*., 2007). Various works note a possible ratio of bladder cancer risk/duration of exposure to chlorinated surface waters (Villanueva *et al*., 2004), but no firm conclusions exist (Cantor 1997). Some studies observe an increased risk of bowel cancer with accumulation and degree of exposure to THMs and with the length of time a person has resided in an area supplied with chlorinated surface waters (Hildesheim *et al*., 1998). Other works studied the possible relationship with colon cancer (King, Marrett and Woolcott, 2000), but these works provided no conclusive results. The lack of irrefutable results and the controversy of some of these aforementioned studies on the role of THMs in the carcinogenesis in humans suggest the need to undertake more specific studies to assess this possible association (Ranmuthugala *et al*., 2003).

The objective of the following observational study is to assess the TTHM concentration in the drinking water of the city of Valencia and its possible association with mortality by bladder and digestive cancer. In addition technical aspects are discussed.

MATERIALS & METHODS

In relation to the water supply in the studied city, there are two water treatment plants (points of entry, POE, that correspond to chlorination points); located ~15 Km from the city centre, one in the north (POE-1), involving raw water from the river Turia as the main water source) and other in the south (POE-2), involving water from the river Jucar as the main water source). It should be noted that an excess of raw water before POE-2 is occasionally transported via the Jucar-Turia canal to the entry of the POE-1 to supply the city, depending on water availability and water needs. Raw water before POE-2 is of more quality, e.g. less organic matter (Biochemical Oxygen Demand (BOD) ~0.5 mg/L O_2) and less chlorine dose (BOD ~2 mg/L Cl_2) than the raw water before POE-1 (BOD ~3 mg/L O_2 and ~3 mg/L Cl_2). Then, less TTHM concentrations are expected when the POE-2 water supply is in use. This justifies having to transport water via the Jucar-Turia canal when such water is readily available. Flow rates range between 2.3 and 3.5 m^3 /s (POE-2 and POE-1, respectively). Residual chlorine levels range between 0.4 and 1 mg/L Cl_2 (in the network and POE, respectively). Bromide concentration is almost constant, between 0.2-0.4 mg/L.

The TTHM level on drinking water in Valencia, distributed along the water supply system (tap level) was studied. Two data sets were considered: (i) 61 data from an eight-year study (2000-2007) involving conventional sampling frequency (set by the regional water company in accordance with the demographic density; where sampling points changes from month to month, covering different sites). (ii) 255 data from a specific high-frequency study over a 16-week period in 2005 (from 20-06-2005 to 6-10-2005), involving 2-8 measurements each day, 3-4 days a week along 16 selected sampling points (see Table 2).

TTHM have been determined by gas chromatography following a procedure described in Standard Methods (6200B) based on purge and trap capillary column with mass spectrometry. The method was validated according to the ISO 17025 accreditation scheme (ISO 17025 2005) incorporated by the testing laboratory, and then an improved quality assurance on method and sample results is guaranteed. The sample collection in the sampling sites was followed applying a recommended protocol in Standard Methods (1060B), similar to that described in previous editions. Each sample was analysed in triplicate. The limit of quantification of the analytical method was 4 µg/L of TTHM (1 µg/L each compound).

The city of Valencia, with almost 800,000 inhabitants is distributed into municipal districts (see Fig. 1). The municipal district was used as basic analysis unit in accordance with the objectives of the present work. 10 districts counting with a reference hospital, from which information on cancer mortality was available, were selected (They are coded from A to H in Fig. 1). Data about the number of deaths in 2005 by bladder and digestive (including several tumours: mouth and pharynx, oesophagus, stomach, small intestine, large intestine, rectum, liver, gallbladder and pancreas) cancers, among the population of each district, were used. The number of inhabitants per district was obtained from the records at the Spanish National Statistics Institute. The available characteristics of the studied populations are shown in Table 1. Information segregated by districts on possible influential factors such us as smoking habit, alcohol consumption, fibre intake and economic status was not available.

To estimate age and sex-specific standardized mortality rates (Jenicek 1995), we used estimated national population data for 2005. This form of standardisation was specifically chosen so that the rates and variation in mortality could be compared without sex and age confounding the results. The STATA program, v 9.1, was used for calculations. The Unscrambler program, v 7.6, was used for multivariate

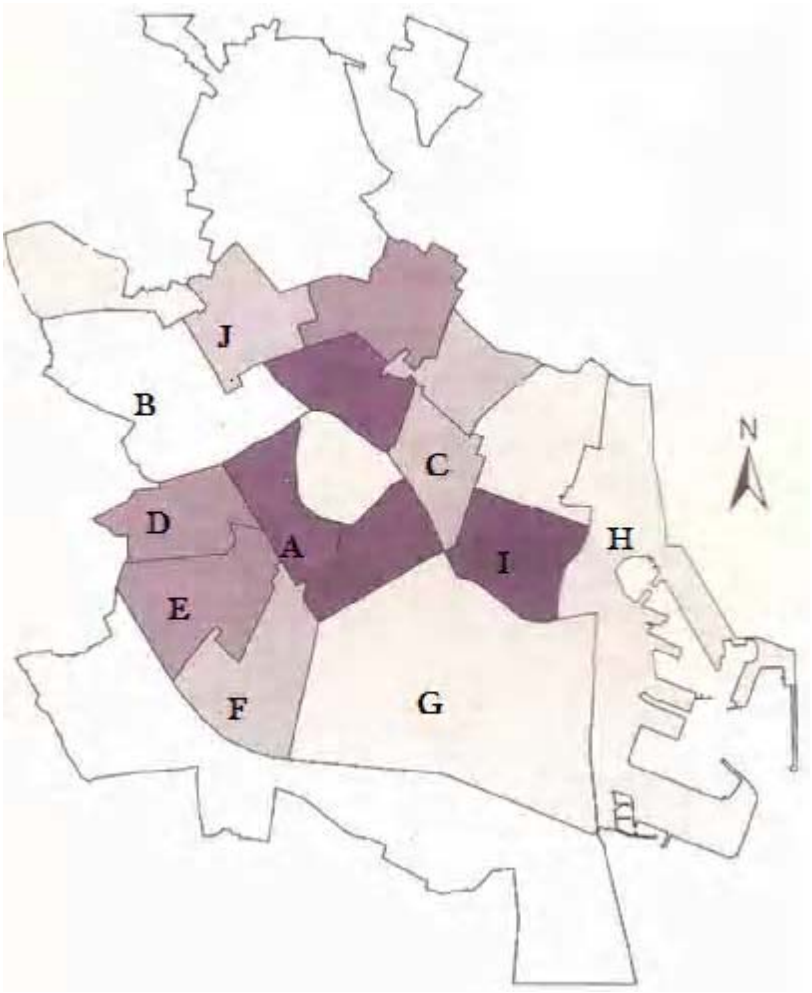

Fig. 1. Studied districts

regression (Partial Least Squares, PLS). The PLS algorithm relates a response variable (**y**-vector) and some predictor variables (**X**-matrix). From autoscaled **y**-**X** data it calculates standardised coefficients (one for each **X**-variable) and their uncertainty intervals using the jack-knife approach (Martens and Martens, 2001), performed during the cross-validation process. These values can be used to evaluate the relative importance of each **X**-variable in describing the **y**-variable (Martens and Martens 2001).

RESULTS & DISCUSSION

Table 1 shows the general available characteristics of the studied population, segregated by district. Gender distribution is normal where women predominate slightly but not significantly. Regarding age, the population was somewhat elderly. The educational level and the economic activity, related to exposure to chemicals, could be considered a priori as influential factors of cancer risk (Borchini *et al*., 2007). Information on these variables is also included in Table 1. It would be also interesting to account with information on other possible influential factors, such as smoking habit and alcohol consumption, a risk factor, or fibre intake, a protective factor against certain digestive cancer types (Hildesheim *et al*., 1998), but data segregated by districts were not available.

We have compared available data for the overall city (Valencia, Valencia community, East of Spain) against other Spanish city (Santiago de Compostela, Galicia community, NW of Spain). The two cities have similar economic status, rent per capita (Ln) 9.7 and 9.5, respectively (Monterrey and Sanchez-Segura 2006), smoking habit (percentages), 34.4 and 31.1, respectively, alcohol consumption (percentages de consumo en 30 días previos a la recolección de los datos), 63.6 and 59.6 respectively, and fibre intake (g per person and day), 17.5 and 15.7, respectively. In contrast, both communities have a different mortality rates (per 100000 inhabitants), by digestive cancer, 225.6 and 108.90, respectively, and bladder cancer, 34.52 and 12.20, respectively. Such differences seem not to be

Table 1. Characteristics of the studied population

District	A	B	C	D	E	F	G	H	I	J	Total
Total	48773 (100.00)	28967 (100.00)	30376 (100.00)	47862 (100.00)	57197 (100.00)	50097 (100.00)	69064 (100.00)	58376 (100.00)	52402 (100.00)	39465 (100.00)	482579 (100.00)
Sex											
Men	22072 (45.25)	13808 (47.67)	14203 (46.76)	22391 (46.78)	27669 (48.37)	24319 (48.54)	33293 (48.14)	25327 (43.39)	25086 (47.87)	19433 (49.24)	227601 (47.16)
Women	26701 (54.74)	15159 (52.33)	16173 (53.24)	25471 (53.22)	29528 (51.63)	25778 (51.46)	35771 (51.72)	33049 (56.61)	27316 (52.13)	20032 (50.76)	254978 (52.84)
Age											
0-24	10961 (22.47)	8322 (28.73)	8415 (27.70)	11318 (23.65)	16754 (29.29)	14001 (27.95)	18380 (26.61)	16040 (27.48)	14051 (26.81)	11412 (28.92)	129654 (26.87)
25-44	14752 (30.25)	8438 (29.13)	9423 (31.02)	15236 (31.83)	19749 (34.53)	16503 (32.94)	23082 (33.42)	18552 (31.78)	18171 (34.68)	13390 (33.93)	157296 (32.60)
45-64	11222 (23.01)	7899 (27.27)	7596 (25.01)	10908 (22.79)	13072 (22.85)	11791 (23.54)	16492 (23.88)	12942 (22.17)	11755 (22.43)	9167 (23.23)	112844 (23.38)
?65	11838 (24.27)	4308 (14.87)	4942 (16.27)	10400 (21.73)	7622 (13.33)	7802 (15.57)	11110 (16.09)	10842 (18.57)	8425 (16.08)	5496 (13.92)	82785 (17.15)
Education level [a]											
Low	18700 (43.04)	14199 (53.52)	8638 (32.21)	27406 (64.12)	28876 (56.18)	28975 (63.70)	38618 (61.43)	36431 (71.21)	28802 (59.33)	23998 (67.49)	254643 (58.60)
Middle	10966 (25.24)	6684 (25.19)	6730 (25.10)	9502 (22.23)	13428 (26.12)	10737 (23.61)	14625 (23.26)	9937 (19.42)	11625 (23.95)	7950 (22.36)	102184 (23.51)
High	13782 (31.72)	5649 (21.29)	11450 (42.70)	5834 (13.65)	9098 (17.70)	5772 (12.69)	9623 (15.31)	4793 (9.37)	8121 (16.73)	3609 (10.15)	77731 (17.89)
Total	43448 (100.00)	26532 (100.00)	26818 (100.00)	42742 (100.00)	51402 (100.00)	45484 (100.00)	62866 (100.00)	51161 (100.00)	48548 (100.00)	35557 (100.00)	434558 (100.00)
Economic activity [b]											
With exposure to chemicals	5677 (30.92)	4660 (39.13)	3139 (25.59)	8582 (48.28)	10918 (45.06)	10404 (51.11)	13553 (48.15)	11252 (52.92)	10481 (46.81)	9291 (56.52)	87957 (45.54)
Without exposure to chemicals	12685 (69.08)	7249 (60.87)	9129 (74.41)	9194 (51.72)	13314 (54.94)	9951 (48.89)	14596 (51.85)	10011 (47.08)	11908 (53.17)	7147 (43.48)	105184 (54.46)
Total	18362 (100.00)	11909 (100.00)	12268 (100.00)	17776 (100.00)	24232 (100.00)	20355 (100.00)	28149 (100.00)	21263 (100.00)	22389 (100.00)	16438 (100.00)	193141 (100.00)
Interdistrict movements (%)	4.17	3.68	3.95	3.06	2.79	2.78	2.85	2.51	4.08	2.96	3.28

[a] Population >10 years.

[b] Population working. With exposure to chemicals (agriculture, fishing, construction, industry, mining and machinery)

explained by the above factors; however, are consistent with the TTHM leves (µg/L) in both communities, 44.36 in Valencia (mean of our results) and lower than 32.00 in Santiago de Compostela (Monterrey and Sanchez-Segura 2006). Inter-district movements (a confounding factor) are relatively low (< 4.2 %), therefore, its influence could be neglected. A typical limitation of such types of studies is the latency period, i.e. ideally cancer data should be related to data of TTHM collected 20-30 years ago. Unfortunately analytical results from such period are not available (a general problem). Then it must be assumed that recent TTHM data could be used as valid indicators of possible cancer TTHM association. Fig. 2 shows the TTHM concentrations, segregated by districts, corresponding to the 8-year study according to the established sampling plan, characterized by low frequency analysis and disperses sampling sites. The main observation is that there is high variability related to this parameter (e.g. standard deviation, *SD*, is up to 29 µg/Las in districts B and C, which shown the largest median values). Also, the number of available data per district is heterogeneous.

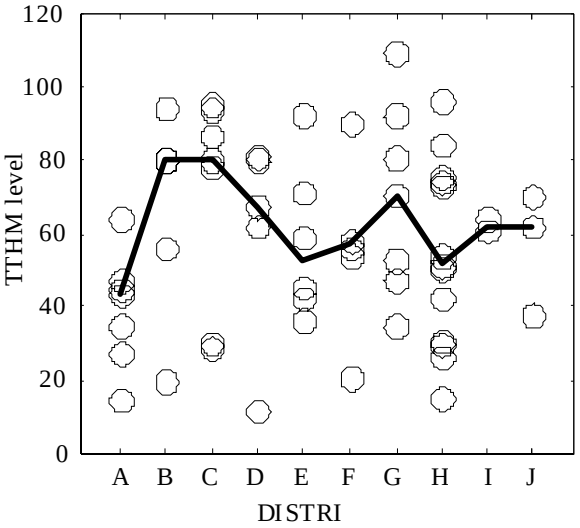

Fig. 2. TTHM concentrations (o) in the 10 selected districts along eight years according to the established sampling plan. The median is highlighted (line)

Such TTHM data could be useful in terms of quality control schemes (e.g. to verify if the overall water quality in the city agrees with the legal EC TTHM level, 150 µg/l, this value is valid until 1 January 2009, when the level will decrease to 100 µg/L). However, they are less convenient for epidemiological studies, particularly, for the one proposed here centered in the between-districts variability. The high *SD* values are consistent to the fact that water of different quality (from POE-1 and POE-2) is mixed, and final quality may vary between months and years. Available data in a short-period (16 weeks in 2005), characterised by high sampling frequency and fixed sampling points, could reflect more consistently the between-districts variability on TTHM levels. Table 2 displays the *mean* concentrations of the TTHMs of each district, as well as other statistics. As can be seen, *SD* values are lower (from 8 to 17) than before and the number of samples per sampling site is homogeneous. Some districts were sampled at different sampling sites to have an idea of the between-sample site variability inside a district. Although the data still reflects a large intrinsic variability (e.g. see maximum and minimum values in each sampling site), the *mean* could be a reasonable good indicator of TTHM level; at least better than the *median* value from Fig. 2.

In order to account with an external invariable reference we have include in Table 2 the POE-1 to district length of the distribution network. TTHM level can be expected to increase with prolonged post-disinfection time, which is often related to distance (Bove, Rogerson and Vena, 2007). Then this variable could be used as indirect indicator of TTHM level. Some variables from Table 1 were also included in Table 2 (The percentage of people working with exposure to chemicals and the percentage people with the lowest education level), since a priori, possible association with cancer could be expected for them (King, Marrett and Woolcott, 2000). Finally, the available data of the mortality rates by digestive and bladder cancer segregated by districts was shown in Table 2. Separated data for women and men are included. Comparisons were possible since mortality rates were standardized (Jenicek 1995).

Variables in Table 2 were submitted to multivariate regression analyses. *TTHM* (*mean* values), *LENGTH*, *WORK* and *EDUC* were used as descriptor variables (**X**-data matrix). The individual mortality rates were used as response variables (**y**-data vector). Variables *WORK* and *EDUC* exhibit high positive correlation, while *TTHM* and *LENGTH* show some positive correlation. To avoid collinearity problems PLS regression was used (Martens and Martens 2001). Initially 2 PLS factors (or latent variables, VLs) should be expected according to the correlations between **X**-variables.

Inconsistent models (e.g. null or low descriptive ability of the **y**-variable) were encountered (results not shown) for all cancer data except for one. The only reasonably consistent result was for bladder cancer in women (see Fig. 3). The PLS model with 2 LVs (a consistent result) explains 78% of the variability this cancer data (a relatively high value); although it is favoured by the leverage effect of the district (H),

Table 2. Data related to sampling points and districts. Statistics related to TTHMs (µg/L) per sampling points. Length (m) of the water distribution network. Percentage of people working with exposure to chemicals (*WORK*). Percentage of people in the lowest education level (*EDUC*). Standardized mortality rates for digestive and bladder cancer (direct method) per 100000 inhabitants

DISTRICT	TTHM					LENGTH	WORK	EDUC	DIGESTIVE CANCER			BLADDER CANCER		
(Fig. 1)	COUNT	MEAN	SD	MINIMUM	MAXIMUM				MEN	WOMEN	TOTAL	MEN	WOMEN	TOTAL
A	15	26.2	8	9.6	47.8	37857	30.92	43.04	362.5	250.9	301.4	72.5	0.0	32.8
	15	34.6	12	15.0	53.1									
B	16	52.5	13	35.4	77.5	65573	39.13	53.52	195.5	151.7	172.6	36.2	6.6	20.7
	16	52.2	17	17.4	77.1									
	16	49.7	13	32.2	73.4									
C	16	51.3	13	34.4	82.6	30108	25.59	32.21	309.8	179.3	240.3	70.4	6.2	36.2
D	16	43.9	12	23.2	62.1	50941	48.28	64.12	424.3	176.7	292.5	67.0	7.9	35.5
	16	33.3	17	8.7	61.3									
E	16	42.4	14	20.1	67.2	52184	45.06	56.18	180.7	105.0	141.6	28.9	3.4	15.7
F	16	45.6	11	20.2	63.2	44820	51.11	63.70	238.5	143.5	189.6	94.6	0.0	45.9
	16	32.8	13	15.7	61.4									
G	16	48.4	15	24.5	73.4	77612	48.15	61.43	258.3	153.8	203.9	45.1	2.8	23.1
H	16	52.6	11	38.0	73.6	128744	52.92	71.21	438.3	233.0	322.1	79.0	24.2	48.0
	16	56.3	14	34.4	84.9									
I	16	46.3	9	33.0	59.6	47332	46.81	59.33	219.3	175.7	196.6	59.8	3.7	30.5
J	16	41.6	13	23.3	70.0	37845	56.52	67.49	241.9	149.8	195.1	36.0	0.0	17.7

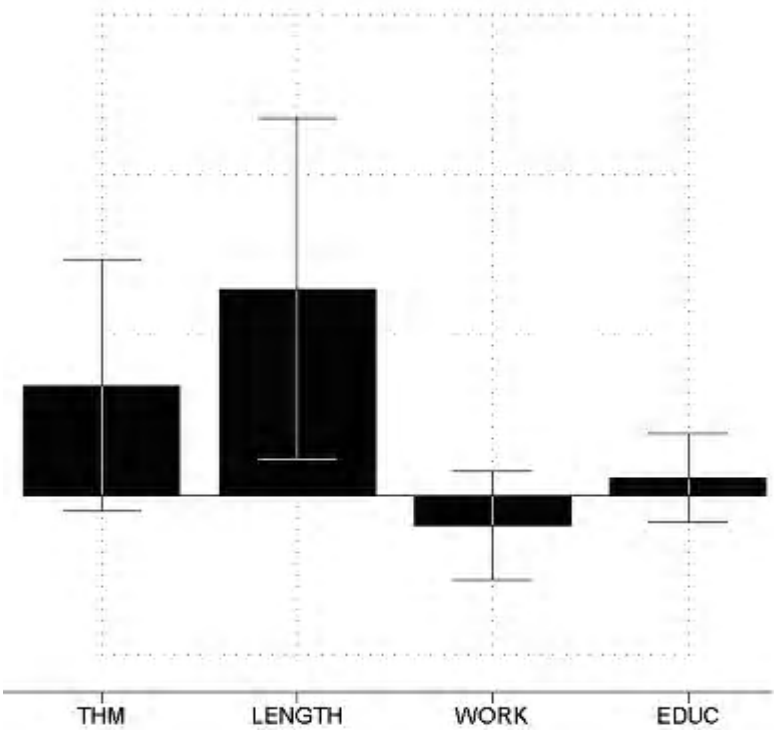

Fig. 3. Standardized PLS coefficients and uncertainty intervals for predictor variables

particularly due to its high length of the distribution network Table 2). As can be observed, the coefficients related to indices of trihalomethanes (*TTHM* and *LENGTH*) have larger coefficients than *WORK* and *EDUC*. However, only the *LENGTH* variable exhibits a non-zero uncertainty interval (again influenced by district H). If one of the sampling points of district D (33.3 μg/Lin Table 2), which exhibit a relatively low value and is bad predicted by the PLS model (e.g. outlier; the PLS model predicts a higher value for this district, as occurs for the other available district D sample, 43.9 μg/L), the *TTHM*-coefficient becomes significantly above zero (in view of its uncertainty interval). These results suggest that, according to the current available data, thrihalomethanes could have some influence on this particular bladder cancer risk on women's population. Although the present study cannot demonstrate unequivocally this relationship, at least, reveal that more studies in this direction are justified.

The TTHM level-women's mortality rate relationship (using the experimental *TTHM* variable) is illustrated in Fig. 4. Except for district D (in which one of the two sampling sites shows inconsistent results; the same indicated above), an apparent direct nonlinear relationship seems exist between women bladder cancer incidence and the THM level. Again, this relationship should be considered provisional (i.e. it would need future experiments to be confirmed). Under this assumption, it suggests that the risk of women's mortality rate could start above 40 μg/L of TTHM, well below the EC level (150 or 100 μg/L).

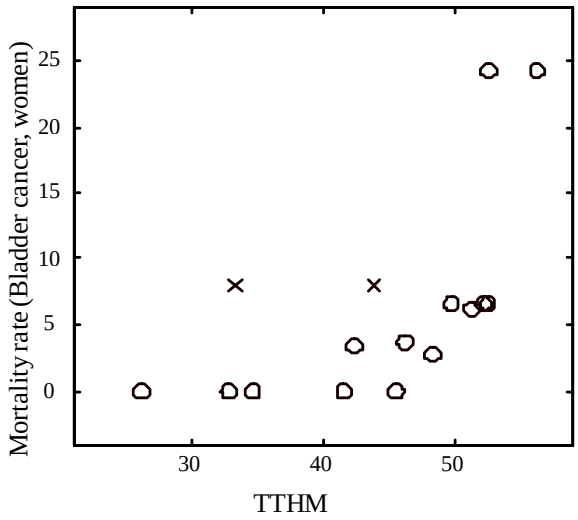

Fig. 4. THMs level-women's mortality rate (bladder cancer) relationship. The two sampling points of district D has been labelled as ×.

CONCLUSION

Certain controversy exists in the literature related to studies which found a risk of bladder cancer associated with levels of TTHM. In contrast, TTHMs-cancer association is consistent with recent toxicological data and animal bioassays. Therefore, confirmation (at

least, particular observations, trends, and hypothesis) must have partial relevant public health implications in relation to preventing exposure to these water contaminants. Our results suggest that a possible association exists, but related to bladder cancer mortality in women (in men is not observed, which could advise that it could be masked by other factors). However, in our opinion, the main conclusion is that the risk of cancer in relation to the TTHM levels (significantly lower than those currently regulated), still deserves more attention. However, this implies careful experimental designs (e.g. high frequency analyses) and multivariate studies to account with possible factors involved. Such data accumulated with time (to overcome the latency period limitation), could serve to obtain definitive consistent relationships. On the other hand, we suggest that further studies should include (when possible) available data on other DBPs, apart from TTHMs, in order to obtain more relevant results on the individual contribution of such compounds. The present results (as an provisional alert) suggests that it would be convenient to review the current sampling plans, the TTHM levels allowed and to observe the cancer evolution rates in individual areas, particularly those with risky features; say, spring surface water and/or high organic matter content, as those in the Mediterranean zone.

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