Author's response to reviews

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

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Author's response to reviews: see over

Reviewer's report

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

Version: 1 **Date:** 1 February 2007

Reviewer: Richard W. Clapp

Reviewer's report:

General

This is a potentially useful article that will contribute to the understanding of environmental risks from incinerators. It needs considerable work before it is of publishable quality, however.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The exclusion of 9 cases, described on page 6, is not well-supported. If the cases moved to the area after 1969, they could still have had substantial exposure. Figure 1 indicates that the peak year for incinerator emissions were in the late 1970s. It would be of interest to know how the risk estimates changed with the 9 cases (and their controls) left in the dataset.

Table A shows results for the population including the 9 cases of subjects who moved to the province of Venice after 1969; in total, 181 cases and 430 controls. The matched cases are 25; 2 were excluded for malignant tumour. The ORs do not change with the inclusion or exclusion of these subjects. We decided to exclude them because we cannot assign an exposure value for the periods of residence outside the province of Venice, since we have no information available on incinerators in other provinces. However, we know that the Veneto region was the first in Italy to build incinerators at the end of the 60s and the industrial area of Venice (Porto Marghera) was the first industrial zone in Italy and was built right after the Second World War. Subsequently, many incinerators and waste plants were built in Italy, therefore a subject might have been exposed in places other than the province of Venice. For instance, one of the 9 subjects excluded from the study moved to the province of Venice on 10 April 1975; for the entire period outside the province, 1.1.1960 – 9.4.1975, we have no exposure data: it is likely that the subject was not exposed until about 1970, wherever the subject lived at the time, but for the following period we cannot exclude exposure in other provinces.

Table A – ORs and corresponding 95% CI of sarcoma in both sex, all sites, according to length and levels of exposure (fgr/m^3). Cases = 181; controls = 430 (Including 9 cases and relative 25 controls not continuously residents in the Province)

Average exposure (fgr/m^3)	**Length of exposure (years)**		
	< 32	>= 32	All
	Cases/Controls	Cases/Controls	Cases/Controls
	OR (95% CI)	OR (95% CI)	OR (95% CI)
< 4	13/43	45/123	58/166
	1	**1.61**	**1**
		(0.71 – 3.63)	
4-6	44/107	42/98	86/205
	1.67	**1.91**	**1.27**
	(0.76 – 3.68)	(0.84 – 4.34)	(0.84 - 1.91)
≥ 6	17/31	20/28	37/59
	2.57	**3.3**	**2.08**
	(0.95 – 6.92)	(1.24 – 8.76)	(1.19 - 3.64)

ORs and 95% CI are the same as in table 1

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author
can be trusted to correct)

- In the first sentence of the abstract, the term "environmental doses" is used; the typical language is "environmental exposures," since dose implies a biological measure. This study really uses modelled exposure values for subject residences. The sentence has been corrected.
- The Conclusions statement in the abstract, at the bottom of p. 2, is too strong and should say "Our study supports the association between modeled dioxin exposure and sarcoma risk. The statement has been changed as recommended.
- There are such chemicals as polybenzofurans (mentioned on p. 3 and in the list of abbreviations), but the contaminant of concern with incinerators is polychlorinated dibenzofurans (PCDFs). We only assessed PCDDs and PCDFs. The text has been corrected.
- The authors describe the study as "a registry based case-control study" on p. 3 but it is more accurately called a "population-based case-control study," with cases from a population-based cancer registry. The controls are from the general population files, as described on p. 4. The description of the study has been corrected.
- "Mesotheliomas" is mis-spelled on p. 4. The spelling has been corrected.
- The word "inexistent" should be "non-existent" on p. 5. The word has been replaced.
- Gauss Boaga representations (p. 5) should be explained; this is not used widely. We have modified the text
- The text says thirty three incinerators were studied, yet Table 1 only lists 31. Some of these are called power stations and one is called "Aluminium" - are these really incinerators? We have now specified the number of incinerators and the other types of industrial sources of dioxins.
- The term "fentograms" should be "femtograms" throughout the text. The spelling has been corrected.
- Two cases excluded on p. 6, e.g., the "radio-induced case" and "von Rechlinghausen's disease" are mis-characterized or mis-spelled. Presumably the first is "radiation-induced," and the correct spelling of the second is usually spelled "von Recklinghausen's disease." The wording has been corrected.
- The Results and Discussion section should be separated into "Results" and then beginning on the bottom of p. 8, "Discussion" beginning with "A few observations should be made. . ." . We have separated the sections and the Discussion section begins one paragraph prior to the point suggested.
- On p. 8, the abbreviation LC is used, where it seems to be Confidence Intervals or CI that is being presented. In the list of abbreviations on p. 15, there is a definition of CL, which is called Confidential Limit -this should be either Confidence Limit or CI, Confidence Interval, and should be consistent throughout the text. We have now used CI throughout.
- The discussion goes on for five pages and includes some text about the SatScan statistic results (p. 10) which should have been introduced in the Methods and presented in the Results sections. These results refer to Figure 2, but it is unclear how the statistic is reflected on the map. This needs to be made more clear or else eliminated from the text altogether. The cluster analysis has been moved to the “Methods” section and Figure 2 has been changed and shows the study area, like Figure 1.
- On p. 12, the argument regarding older subjects and prior work experience is unclear. The text needs to be reconsidered. Changes have been made accordingly.
- On p. 13, the critique of Tuomisto, et al. is incomplete and probably unnecessary. It could simply be stated that Tuomisto, et al. found no association in their study. Changes have been made accordingly.
- On p. 13, the term non-HD lymphomas is used, when the current terminology is non-Hodgkin lymphoma. Changes have been made accordingly.

- The Conclusions section is a single, confusing sentence. It seems to begin as a statement about the study and ends with a policy recommendation. It can be simplified and limited to the authors' summary of the study. The Conclusions have been changed following reviewer suggestions.

Discretionary Revisions (which the author can choose to ignore)
There are numerous mis-spellings and punctuation errors in the text which should be reviewed and corrected.
Unable to decide on acceptance or rejection until the authors have responded **What next?:** to the major
compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Reviewer's report

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

Version: 1 **Date:** 2 February 2007

Reviewer: Jean-Francois Viel

Reviewer's report:

Major Compulsory Revisions

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1. Page 5, lines 16-19: Since exposure assessment is always a crucial point in environmental epidemiology,more details are absolutely needed. In this respect, the second half of page 9 should be moved here, while needing deep clarification. For example, the sentence "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" is unacceptable. The reader don't have to take this point for granted. If the assessment was based on assumptions, extrapolations, expert judgments, etc. (and why not), it must be clearly specified. We provided details in the manuscript about the work carried out to identify the sources of emission and reconstruct the historical data on plant operations.

2. Page 7, 5th paragraph: Table 4 lacks consistency, so I have replicated the results (although unconditionally) to shed some light. On the one hand, the authors carry out separate tests for trend (< 32 and ³ 32 years of exposure), and on the other, they combine both groups to estimate ORs per categories (by using a single reference category, i.e. "length of exposure < 32 and average exposure < 4"). Why?

Table 4 can therefore appear misleading, since the OR of 3.30 is somewhat overestimated by using as reference category "< length of exposure < 32 and average exposure <4" instead of "length of exposure ³ 32 and average exposure < 4". In the latter, I obtain an estimate about 2.05 (still significant). Moreover, according to my results, tests for trend seem to result from logistic regressions in which exposure has been introduced in a quantitative way (ascribing the values 1, 2 , 3 to the categories). This is a strong assumption which must be explained in the "Statistical analyses" section.

We redesigned Table 4 (now Table 1), which now shows the joint effect of average (fgr/mc) and length (years) of exposure, so we dropped the test for trend. The reference category is: average <4 fg/mc and length < 32 years. The χ_1^2 Wald test for trend was used only for the tables in which the average exposure is stratified by sex or ICD-IX code.

3. Pages 7 and 8: Combinations by cancer sites, length of exposure, morphological groups, and exposure levels are so numerous that the manuscript gets untidy (and the likelihood of false positive results increases…). There should be a greater amount of logic and structure in the flow of these results. A drastic reduction of the "Results" section is compulsory. Morphological analysis has been left out for improved clarity.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

4. Page 3: Some rationale on the hypothesis under study is needed. Why has the survey been launched: to replicate the paper by Comba (ref 4)? Because a cluster had been previously highlighted? Because of a lay press report? At the request of some local authorities? Etc .We provided an explanation in the introduction.

5. Page 3, second paragraph: Quoting only the paper by Steenland (ref 2) yields a one-sided overview of the recent controversy surrounding the carcinogenicity of dioxin. For a balanced overview, at least two further papers must be quoted:

Cole et al. Dioxin and cancer: a critical review. *Regulatory Toxicology and Pharmacology* 2003;38:378-388.

National Academy of Sciences. Health risks from dioxin and related compounds. 2006. The two articles have now been quoted.

6. Page 3, last paragraph: The description of the study area is unclear. Why is not the whole Province of Venice studied since it seems to be wholly covered by a cancer register? Why and how have the three Local Health Units been chosen? Figure 2 should be mentioned in this paragraph (and therefore become Figure 1). A description of the study area has been added (it is represented now in Figure 1). It includes about half of the province of Venice, since the Registry does not cover the other half.

7. Page 4, lines 16-17: Who has revised diagnoses: a blinded clinician? What does "almost always available" mean (give a percentage)? In the period of diagnosis we considered, ICH was used in case of diagnostic doubt but it was not a routine examination. About half of the cases had ICH, 78 had more than one histological examination and 10 cases had autopsy confirmation. We believe diagnostic quality to be good.

8. Page 4, line 18: Letters and not figures begin sentences. Text has been corrected.

9. Page 4, last sentence: This sentence, stating that sarcomas and non-hodgkin's lymphoma were replaced, contradicts the sentence appearing page 6, line 21, specifying that all types of cancer were excluded. This was a mix-up; we changed the text, removing "and non-Hodgkin's lymphoma".

We had taken from the Tumour Registry database the cases of sarcoma and also those of non-Hodgkin's lymphoma for two studies and we replaced the controls that were also cases. Only after reconstructing the residential history did we exclude the controls that had a malignant tumour and these were not replaced.

10. Page 5, lines 14-15: To which extent can electricity power stations and refineries be considered as incinerators? Should not the word "incinerators" be replaced by "industrial sources of airborne dioxin" or something similar (don't forget to change the **title** accordingly)? Moreover, the acronyms RSU and RO do not match their corresponding descriptions. Corrections have been made addressing these observations.

11. Page 5, lines 9-11: This point should be detailed earlier in the draft (see comment # 3). Text has been changed .

12. Page 5, line 20: Is not "The Long Term ISC model" the Industrial Source Complex Model (ISC3) operating in long-term (ISCLT3) mode? Changes have been made accordingly.

13. Page 5: Surprisingly, Table 1 is mentioned neither in this page nor in the rest of the manuscript (appearing only as an annex). However, since the manuscript lacks conciseness I would recommend to withdraw it. We removed Table 1 (page 6, line 3)

14. Page 6, "Population on analysis": this section should be embedded in the "Selection of cases and controls" section. Moreover, since it is sufficiently detailed I would recommend the withdrawal of Table 2. Table 2 has been removed. We left the section "Population on analysis" because the exclusion of part of the subjects only took place after the reconstruction of the residential history of all the selected subjects and the assessment of pollution over time.

15. Page 7, 2nd paragraph: How have the numbers of classes and the cut-points been determined? We identified 3 classes of exposure intensity by estimating the OR curve as a function of the level of exposure used as a continuous variable; the points at which the curve slope changed were taken as cut-off points. It is explained in the text.

The sentence "Table 3 shows the distribution of cases in the sub-groups analysed" should be moved to the "Results" section. Table 3 has been removed.

16. Page 7, 3rd paragraph: Confidence limits (CL) are the lower and upper boundaries of a confidence interval (CI). Although CIs are usually reported (including in "Environmental Health", as stated in the instructions for authors: "Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals"), if the authors want to stick to CLs, they must replace the expression "CL 95%" by "95% CL" throughout the manuscript. Moreover, "conditional (and not conditioned) logical regression" is the right term. Which software has been used? The text has been changed and CI has been used throughout. We have explained in the text which software we used.

17. Page 7: A subtitle "Statistical analysis" would help. A subtitle was added as suggested.

18. Page 7, “Results and discussion” section: The Results and Discussion may be combined into a single section in manuscripts submitted to Environmental Health or presented separately. For the sake of clarity, I strongly encourage the authors to separate the two sections. Text has been changed accordingly.
19. Page 8, 3rd paragraph: It should appear at the beginning of the “Discussion” section. The paragraph was moved accordingly.
20. Page 8, 5th paragraph: Too vague, it must be rephrased. The sentence was rephrased.
21. Page 10, 2nd paragraph: The ISC3 dispersion model description must appear in the “Methods” section. Text has been changed accordingly.
22. Page 10, second half: New results are reported although “facts” must be clearly separated from their interpretation. These results must be moved either to the introduction (if they represent the starting point of the case-control study) or at the beginning of the ”Results” section. Text has been changed accordingly.
23. Page 11, last paragraph: “There is no reason to suppose that the eating habits of the case are very much different from those of the controls”. However, local communities whose diets consist significantly of foodstuffs grown/reared in the vicinity of an incinerator may have significantly elevated serum dioxin concentrations and such local food consumption might be linked to individual characteristics (incomes,socio-economic status) not accounted for in the analyses. Following these observations, the statement has been modified.
24. Page 12, lines 13-14: This sentence is unclear. The sentence has been rewritten.
25. Page 12, line 15: “The higher risk observed in women” is somewhat excessive. The risk is of similar magnitude. We changed the text, underlining that the excess of risk is statistically significant for women and not for men.
26. Page 12, last paragraph: References 18, 19, 20 do not deal with dioxin exposure. These references have been dropped.

Discretionary Revisions (which the author can choose to ignore)
27. Page 3, third paragraph: TEQ have just been revised. Obviously, the authors are not to be blamed for using TEQ1998, but they could mention this new fact and quote the following paper:
Van den Berg M et al. The 2005 World Health Organization re evaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 2006;93: 223-241.

Unable to decide on acceptance or rejection until the authors have responded **What next?:** to the major compulsory revisions
Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.