

## Reviewer's report

**Title:** Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up

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### Reviewer's report:

There are several questions that should be answered:

- 1) There is no explanation on why the period of observations stops in 1996, more than ten years ago.
- 2) It is noteworthy and reassuring that the risk ratios of all cancers are very close to one in all zones (notion of zone A with a slightly increased overall cancer incidence is futile, p. 11). The lymphatic and hematopoietic tissue malignancies seem to be the most probable positive finding as in previous studies, although this is a mixed bag, and reliability in zone A suffers from very small numbers. Among these multiple myeloma and myeloid leukemia seem to be the most consistent. Even with these, one wonders that if the risk in zone B is true, should the elevated risk in zone A not show up at fivefold median exposure.
- 3) There were no cancers in subjects with chloracne (abstract and p. 8). Even if the expected number was also low, this is a noteworthy finding. At the same rate with zone B and zone R there should have been about 10 cancers among 183 persons. So the age structure was probably different? Did you estimate the expected age-standardised number? If a true positive association is claimed for TCDD (a non-genotoxic carcinogen in animal studies), one should expect a clear dose-response, i.e. much higher risk at higher doses. The proposed mechanisms imply that high doses (relative to other toxicity) are needed, therefore a linear assumption may not hold. The highest levels especially in children were extremely high, but the average dioxin levels in Seveso areas B and R have not been very high, e.g. Baltic fishermen have higher concentrations of dioxins (as TEQ) than Seveso B population on average (median 170 pg/g, maximum 420 pg/g, with DL-PCBs included median 290, max. 880, resp., Kiviranta et al, EHP 2002, 110:355), still their cancer rate is marginally lowered although for lymphoid and hematopoietic malignancies the point estimate was non-significantly increased (Turunen et al, Int J Epidemiol 2008, 37:1008). There may be reasons for this (e.g. fish consumption), but the difference should be discussed. In fact, the reference level should also show the total TEQ to enable true comparison with other groups (of course all groups should show the total TEQs, but the error is by far largest in the reference group). A normal dose-response paradigm requires that these kinds of discrepancies are carefully discussed.
- 4) The increased risk of breast cancer at the latest period raises questions. The number of childbirths and breastfeeding clearly decrease the risk of breast

cancer. Did the accident decrease the numbers of giving birth in the exposed population?

5) Was the TCDD concentration measured in any of the cancer victims (even at autopsy)? If not, why not?

6) Much greater amount of chlorophenols than dioxins were released in Seveso accident (abstract and p. 8 in beginning of the discussion). The acute chlorophenol exposure was probably quite high, they are easily absorbed through skin. Hence it was NOT a pure TCDD accident. There is some evidence that chlorophenols are also carcinogens (cf. Lampi et al, Scand J Work Environ Hlth 2008, 34:230, IARC vol 41, 1986). As dioxins are fairly weak carcinogens in occupational cohorts, probably even weaker than previously believed (Aylward et al, Risk Anal 2005, 25:945) one has clearly to discuss the dose-responses of both dioxins and chlorophenols very carefully, especially remembering that there were no cancers in the chloracne group.

7) In p. 4 the half-life is estimated at 7.8 years. Several studies (Aylward et al, J Exp Anal Environ Epid 2005, 15:51, Geusau et al, Arch Toxicol 2002, 76:316) have shown that after high exposures half life is much shorter. What implications might this have for the present study? It clearly changes the interpretation of the four industrial cohorts mentioned in p. 8.

8) In p. 7 soft-tissue sarcomas in zone R are said to be 30 % in excess (in fact non-significant). Zone R is a low-exposure area, and at background exposure levels (4 to 145 pg/g) no association has been seen in a relatively large case-control study (Tuomisto et al, Int J Canc 2004, 108:893). The possible relevance should be discussed.

9) P. 9, the published TCDD levels in zone R have been low, and if one believes in TEQs and similar actions of dioxins, with TCDD having no specific effects of its own, the total TEQ levels are barely different from other populations. So what is the basis of expectations that the cancer rates in zone R would in fact tell anything at all on the risks of TCDD? Even if the populations of zones A and B are much smaller, on the basis of what we know now on the mechanism of action of dioxins, the higher dose should cause an order of magnitude elevated risk before one could expect a measurable risk in zone R. It is a bit unfortunate that epidemiologists often think in terms of yes or no, and not in terms of quantitative dose-responses.

10) P. 10 Dai and Oyana study is an ecological study based on soil contamination. There is huge amount of data that dioxin exposure is 80-90 % of food, and food is local to very minor extent (especially in America). Therefore these studies should be taken with great care. Without measured concentrations, it is very soft data.

There is an understandable tendency in this paper to prove the point suggested by the previous studies of the group, but perhaps one should try to make an objective and unbiased analysis considering all of the relevant information gathered on dioxins after the previous studies (as well as the IARC evaluation). It is not always clear from the text, if the increases described are significant (esp. zone A). It is noteworthy that in table 3 there are more than 100 statistical

analyses, by chance alone 5 or 6 of these would give a significant result. The dose-response considerations would be useful if redone considering the changed status of the industrial cohorts due to much shorter half-lives than previously believed (even 1-2 years) which means that, in fact, the levels in the cohorts were remarkably higher than was believed in the previous assessments.

As suggested also by the highly variable concentrations in the Seveso population, existence of TCDD in the environment as such does not tell much of human exposure with the possible exception of small children who were exposed in the backyards. In adult population dioxin exposure is almost exclusively from food, and one should then consider how much of food was local, how much was from shops and originating most likely far from the accident area. Exposure data is often the weakest point in epidemiological studies, and this should therefore be discussed as thoroughly as the patient data to inform the reader about the basic facts and uncertainties.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests