Author's response to reviews

Title: Fertility in four regions spanning large contrasts in serum levels of widespread persistent organochlorines: a cross-sectional study

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Version: 4 Date: 20 October 2005

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Manuscript ID 1153717813768002

**Author response to letter from the editor October 19th 2005 (following first revision).**

Our point by point answers are in yellow and actual changes made in the manuscript have been indicated by the this colour.

1) I recommended including information about the association between the PCB and DDE exposure and semen quality and TTP. Were there correlations? Otherwise no geographical differences could be expected.

OK, we did not understand the introductory remarks of the second reviewer as a request to include data on associations we observe in the present data set between POPs and semen quality/time to pregnancy at the individual level. In all circumstances, this paper is explicitly about regional differences and all analyses are performed from this point of view. The next step will be to examine exposure-response associations at the individual level – but for this we need several separate full papers and we do not think it is feasible or at all possible to provide these analyses in this paper. For clarification we have added the following sentence to the introduction:

In subsequent papers we examine associations between POP concentrations in serum and functional as well as biological indicators of fertility at the individual level.

2) In the introduction the authors state that there are no strong epidemiological evidence for relation between endocrine disruptors and male reproductive disorders. The reader is referred to two reviews one about PCB and a general (Storgaard reference 4 and 5 are identical) reference. There are however other publications showing a more convincing associations.

We apologize. Reference 5 incorrect. Has been substituted by the correct one, the most recent review by Vidaeff and Sever (In utero exposure to environmental estrogens and male reproductive health: a systematic review of biologica Vidaeff,A.C.; Sever,L.E). We believe this paper provides an independent and balanced review of current evidence and clearly calls for research as presented in this paper.

With respect to ‘no strong epidemiological evidence’ we acknowledge that we are addressing environmental xenobiotics (and not for instance DES and the like). Probably most researchers in the field will agree that here the human evidence is indeed very sparse.
Although experimental research offers some support to the hormone hypothesis, the epidemiological evidence on effects of xenobiotics mimicking hormones remains scarce. 

3) The authors have repeated the analyses among nulliparous women; I would like to have the exact FR for the three centres (not Swedish data) as suggested below Table 2. In addition, nulliparous Swedish women had reduced fecundity compared to the others which is explained by a small sample size. It might however be a true finding, since these women are highly exposed and directly comparable to women from the other centres. Most of the Swedish women were interviewed retrospectively about pregnancies occurring many years ago and most of them were successful more than once in achieving a pregnancy. So they are expected to be more fertile. In addition, calendar time trends may explain the differences.

We have provided the adjusted FR with 95% CI for nulliparous women as a footnote to Table 4 (we don’t se that this information fits into Table 2?). The remarks are well taken and hopefully now more clearly acknowledged in the discussion

4) No differences in semen quality were found. This might be caused by selection, if participation is related to poor semen quality. A higher participation rate in Greenland may therefore have included more men with good semen quality thereby overestimating the semen quality in Greenland compared to the other countries.

We have discussed the possible selection problems extensively and the available data (Table 5) do not indicate that subfertile men participate to any substantially higher degree.

5) In the conclusion it is stated that biased findings cannot be ruled out. This could be rephrased stating that the findings could be due to differences in recruitment, reproductive disorders and contraceptive use between countries.

We agree that possible bias for these reasons is a concern that should not be underrated. We have rephrased the conclusion as suggested:

… but the regional variation can also be due to differences between regions with respect to recruitment, reproductive disorders, sexual behavior and use of contraception.

6) The Warsaw sperm count did not have a CI but a ? - please explain and correct. Also, there were two superscript b's in this table.

Errors have been corrected
We would like you to address these additional comments in the form of a revised manuscript, together with a point by point response to the comments from both reviewers. We will then be happy to consider the paper further for publication. Again, we would like to point out that, although Environmental Health as a web-based journal does not have any space restrictions, we suggest that all authors aim at manuscripts that are as short as possible in order to attract the greatest amount of readership attention.

We hope that we have complied with this request by the cuts made from the first to second version.

As already indicated, your revised manuscript should be in strict accordance with our instructions for authors, cf. the pre-acceptance checklist at [http://www.biomedcentral.com/info/edgr-preacceptcheck.asp](http://www.biomedcentral.com/info/edgr-preacceptcheck.asp). Environmental Health is an on-line journal, where accepted manuscripts are used for direct conversion into journal xml format. It is therefore of paramount importance that the manuscript strictly follows the guidelines. The entire paper needs to be double-spaced. DONE, also tables and legends to tables are now double spaced.

On page 6, the single sentence on ethical review does not make a paragraph and needs to be merged or inserted into another paragraph DONE.

An Acknowledgement section is missing. NO, BUT MISPLACED P 25 AFTER CONCLUSION AND BEFORE ABBREVIATIONS. NOW MOVED TO THE INDICATED PLACE AFTER AUTHOR CONTRIBUTIONS.

Please remove blank page 41. CHECKED, NO EMPTY PAGES FOUND?

The tables need to be formatted in strict accordance to EH instructions, please see [http://www.ehjournal.net/info/instructions/](http://www.ehjournal.net/info/instructions/). DONE, to our best knowledge the 7 tables are strictly formatted according the instructions. Titles have been abbreviated and all tables are in portrait layout and with the cells visible.

The same applies to the references, as already indicated. DONE. WE HAVE FORMATTED USING THE BMC REFERENCE TEMPLATE in reference manager 10.0. All references have been checked manually. In press citations have been updated. Reference 18 has been included even this paper is in the process of review at BMC Environmental Health. We hope it will be accepted so this reference can be updated.
In addition, we have noted the recent publication by Spano M et al. (Exposure to PCB and p,p'-DDE in European and Inuit populations: impact on human sperm chromatin integrity) in Human Reproduction. This paper is not included in the reference list. Please clarify the relation between your manuscript and this publication by the same authors.

The Inuendo project is expected to generate several original papers - as we believe we have clearly indicated in the introduction and by the reference to INUENDO and the website. The present paper is together with the exposure profile paper (prof Lars Hagmar corresponding author) that was also submitted to EH are considered the first basic papers. In subsequent publications we are addressing relations between POPs and specific endpoints [TTP, semen quality, sperm chromatin integrity, sexual hormones, X/Y sperm ratio etc, www.inuendo.dk]. The paper by Spano et al is the first paper that has been published – we have updated the reference list to include this paper published in the mean time.

When planning the analysis and publication strategy we of course took care to avoid overlap between publications – and think we have succeed. The two paper submitted to EH are supposed to be the first papers and to create solid references for subsequent papers. The full list of planned publications may be requested.

Yours sincerely,
Jens Peter Bonde

When you have revised your manuscript in the light of the reviewers' comments and made the required changes to the format of the paper, please re-upload the revised files, and make any necessary changes to your manuscript submission forms on the Environmental Health web site, by clicking 'My Environmental Health', logging in with your user name and password and then clicking the manuscript title to go through to your submission screen. You should provide your point-by-point response to the reviewers' comments and the editorial requirements, along with a summary of the changes you have made, by uploading them at the end of the submission process, using the 'Cover letter' box (the cover letter should not be submitted as a supplement).

We would expect you to return the revised paper within three weeks (i.e. by 9 November, 2005), but if you imagine it will take you longer to prepare the revision, please give us some estimate of when we can expect to hear from you.

Please don't hesitate to contact us if you have any problems or questions regarding your manuscript.

With best wishes,

Philippe Grandjean and David Ozonoff