Reviewer’s report

Title: Fertility in four regions spanning large contrasts in serum levels of widespread persistent organochlorines

Version: 1 Date: 9 September 2005

Reviewer: Russ Hauser

Reviewer’s report:

This is a well-written manuscript that explored the relationships between persistent organochlorine pollutants (POPs) and regional differences in several indicators of reproductive health in cohorts from four countries. The methods are generally well described. The authors present interesting data on the demographic characteristics of the four cohorts, the POP exposure levels, and data on measures of reproductive fitness (time-to-pregnancy/fecundity, semen quality). The authors reported between country differences in markers of reproductive health that they hypothesize may be related to between country differences in levels of POPs (PCBs and DDE). The authors offer alternative explanations for these associations, which include potential selection and confounding bias. For instance, there were large between country differences in potential confounders such as lifestyle factors, sexual behavior (e.g., frequency of intercourse for the TTP analysis) and medical histories (e.g., prevalence of urogenital diseases) that may confound the results. In addition, for the semen analyses there are likely differences in raters across countries, potentially dampening associations of POPs with semen quality, if a relationship did exist.

Major Compulsory Revisions

1. Brief mention is made of eligibility/exclusion criteria for the subjects within each country. Further details should be provided to allow readers to determine if there are important differences in the selection criteria between countries. A brief comment is warranted on whether the recruitment setting (e.g., clinic versus hospital) may affect the characteristics of the study population within each country.

2. There are marked across country differences in the mean number of days (232 to 166 days) the women were pregnant at enrollment. The potential for these differences to introduce bias needs to be discussed. For instance, in countries where women were recruited later in pregnancy there may be more ‘missingness’ of women or couples with early pregnancy loss. If the early pregnancy loss were related to fecundity or semen quality this may introduce differences in these measures across countries. Minor: Please present values in weeks (traditional gestational length metric) and provide a measure of variance around the central tendency of the distribution, such as median and 25th and 75th percentiles if distribution is skewed.

3. On page 17, borderline p-values (0.08 and 0.07) should not be used to dismiss potential differences between regions. There should be more discussion of these results, specifically the sperm morphology differences.

4. Page 18, although there were regional differences in fecundability, the statement that it was related to population DDE levels and not PCB levels may be too strong. There are only four data points when country is used as the indicator of exposure.

5. The statement that men in Warsaw had low levels of CB-153 and DDE but could have higher exposures to other compounds should be expanded. Is there evidence of this and if so to what
exposures? Is this based on data or observations not presented here?

6. Page 19-20, the discussion of methodological differences affecting study results is well-done but needs to be further emphasized since it likely accounts for some of the across country differences in markers of reproductive function. Can some of this discussion be moved to earlier in the discussion section and specifically mentioned in the abstract?

7. The tables are generally well-designed and present the data well. The following are brief comments that require minor discussion or minor revisions.

8. Table 1 shows marked differences in participation rates and contraceptive failures across countries (up to 50% in Kharkiv). This raises the concern with bias (i.e., selection and confounding) in the analyses and makes the between country results difficult to interpret. Was participation rate considered as a predictor in the models? This may allow further exploration of whether it was predictive of the outcome of interest (TTP or semen analysis results).

9. In Table 1, the percent participation in the semen sample collection row should be added to the row below number of semen samples collected.

10. Tables 2 and 3 showed marked across country differences in demographics, especially for percent of current smokers (note: there are also likely large differences in number of cigarettes smoked among current smokers), urogenital infections and percent daily intercourse. These marked across country differences again raises issues of concern with inability to adequately control for potential strong confounding by these factors in the between country analysis. This should be commented upon in the discussion.

11. Table 4: The large differences in contraceptive failure rates across countries raise concern with bias introduced by excluding unplanned pregnancies due to across country differences. This should be further emphasized in the discussion.

12. Table 5: Minor point: percentages are row percentage totals. FR changed after adjusting for current female smoking and daily sexual intercourse. This raises the concern that finer adjustment (number of cigarettes smoked or a continuous measure of sexual frequency) may further alter FR. Please comment.

13. Table 7: marked differences are noted in potentially important confounders, e.g., abstinence time, season when sample collected, infections, medication use. This should be commented upon and discussed in the text.

14. Table 8: I was unable to view on screen or print out. The table is corrupted in my version.

15. Figure 11: FR figure, consider the use of log scale for FR.

Minor Essential Revisions


2. Table 7: Spelling: Fever not fewer

Discretionary Revisions

1. Page 23- Future methods that will be used for directly testing the associations between POPs and
markers of reproductive fitness should be briefly mentioned.

2. Table 7: To provide insight into variance about the central tendency of the distribution, present 25th and 75th percentiles rather than 5th and 95th.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**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