Reviewer's report

Title: Maternal occupational exposure to polychlorinated biphenyls and the secondary sex ratio

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Reviewer: Larry Robertson

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The manuscript, entitled “Maternal occupational exposure to polychlorinated biphenyls and the secondary sex ratio” by Carissa Rocheleau and colleagues, describes studies of primiparous birth to mothers who were occupationally exposed to PCBs. The authors conclude “no significant association between the odds of a male birth and mother’s cumulative estimated PCB exposure to time of conception”

The underlying assumption is that PCBs interfere with normal endocrine function and therefore will alter secondary sex ratio. As the authors point out, this basic assumption has “inconsistent support in the scientific literature”, although there is an excellent study in rodents supporting this hypothesis (cited below). Further uncertainties arise from the lack of knowledge of which PCBs, and/or metabolic progeny, may cause this effect, if any will do so in humans. From studies using animals, cells in culture, and purified enzymes, we do know the following related to PCBs and endocrine function:

a) PCBs and OH-PCBs may be agonists and/or antagonists of the estrogen, androgen and progesterone receptors (Arcaro et al., 1999; Bonefeld-Jorgensen et al., 2001; Conner et al., 1997; Fang et al., 2003; Portigal et al., 2002; Schrader and Cooke, 2003; Taylor et al., 2007)

b) Methylsulfonyl PCBs are competitive antagonists of the glucocorticoid receptor (Johansson et al., 1998)

c) PCBs alter thyroid status by several mechanisms (Gauger et al., 2004).

d) Estrogen sulfotransferases and hydroxysteroid sulfotransferases catalyze the sulfation of several endogenous steroids as well as many other compounds. Interactions of xenobiotics with these enzymes may also alter physiologic functions in steroid metabolism through changes in catalytic activity. OH-PCBs may be substrates and/or inhibitors of sulfotransferases (Kester et al., 2000; Liu et al., 2006; Liu et al., 2009) thereby disrupting steroid status.

e) PCBs may increase the expression of aromatase activity (CYP19) in follicle cells (Ptak et al., 2006) and CYP19 and other steroid hormone synthesizing enzymes in adrenal cells (Kraugerud et al., 2010; Li, 2007; Xu et al., 2006).

The authors of the manuscript may wish to expand at the beginning of the
second paragraph in the Background. In place of “Because of their estrogen-mimicking structure”, some of the above (a.-e.) may be mentioned.

In the Discussion the authors may wish to add a reference to the work of Steinberg RM and colleagues, in Biol. Reprod. 2008 Jun;78(6):1091-101. Animal studies with Aroclor 1221 produced a different result. It may be useful to discuss the possible reasons for the differences between humans and rats.

Another consideration is that occupationally–exposed women may have been exposed via different routes of exposure, depending on jobs, (dermal, inhalation), than Yusho, Yu-cheng victims (diet), or the general population (diet or inhalation). Route of exposure may yet prove informative.

Overall a very interesting, informative and well-written manuscript.

**Level of interest:** An article of outstanding merit and interest 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.