Reviewer’s report

Title: A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides.

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Reviewer: Julia Brody

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This prospective cohort study of cancer and pesticide exposures in farm spouses fills an important knowledge gap. Much of what we know about chemicals and cancer comes from occupational studies, but women's employment histories mean they have not historically been included, so less is known about chemicals and cancer in women. This study of wives of pesticide applicators is a creative way to fill that gap.

It adds to the evidence that OC use contributes to some cancers.

The detailed self-report of pesticide use represents a good exposure assessment strategy. Compared with biological measures, it may better represent direct pesticide application exposures rather than exposures to breakdown products from multiple sources (e.g., in the case of DDE as an indicator of DDT exposure). Extensive information was collected on potential confounders.

Line 160-161 and throughout. The statement that most studies of OCs and breast cancer are null is outdated. Most studies of OC residues in older adults are null. However, several reports on early life exposure to OCs provide evidence of an effect on breast cancer from exposure during breast development, which is not complete until the end of the first full-term pregnancy. An important prospective cohort study - the Child Health and Development Studies - has reported higher breast cancer risk associated with certain OCs when exposure was prenatal or under age 14 years (Cohn et al.). The Long Island Breast Cancer Study (LIBCSP) (White et al.) and Sister Study (NIEHOFF et al.) have reported elevated risk in women who recalled seeing or running in the pesticide mist behind fogger trucks as girls. The LIBCSP also reported reduced five-year survival associated with higher OC blood levels at diagnosis (Parada et al.).

Line 171-172. Pesticide applicators were recruited in 1993-1997 when they applied for a license. Would this generally be when they first began applying pesticides? This matters, because the OCs were banned before that time, so this design may not be recruiting highly exposed people. What are the expectations about the life experiences of these women that would have resulted in OC use and exposure during the years of OC use?

Line 302. Please revise. E.g., This is consistent with most studies of residues in older adults.
Line 308. However, please add reference to associations with early life exposure.

Line 312. Why do you think the evidence differs for dieldrin?

Limitations. The discussion of limitations is generally good. However, I am concerned about an additional limitation - complex confounding by age cohort that may result from the timing of the adoption and then banning of the chemicals. For example, the youngest women in this cohort have potential exposure beginning in utero and extending until each chemical was banned. The oldest women do not have prenatal exposure. Table 1 shows that the ever-users of OCs are older, grew up on a farm, and have higher parity. These differences are expected, since OC use occurred earlier in history. Interestingly, more of the ever-users reached menarche at 12 years or less and more have a family history of cancer. Please discuss the interaction of cohort effects and exposure and how this might play out in the analysis. In addition, do you think that growing up on a farm is a good-enough proxy for OC exposure during the years of use? Consider whether there is a natural experiment within this cohort, as in CHDS, comparing women who grew up on a farm and were born before 1948 (about when DDT came into use) or who reached age 14 before that date with those who are younger.

Typo: line 157 change between to with

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