

# Latent Effects of Gestational Exposure to Heptachlor

## Project Scope

Relatively little is known about the effects of heptachlor, a chlorinated cyclodiene insecticide, in humans. Its chemical structure and evidence from animal studies, however, suggest that heptachlor may disrupt hormone function. Heptachlor epoxide (HE), a major breakdown product of heptachlor in the environment, is thought to possess similar activity. A particular area of concern is whether gestational or neonatal exposure can alter neurological, reproductive, or immune functions later in life.

This grant funds research evaluating two primary hypotheses: (1) that heptachlor epoxide exposure during gestation and/or breast feeding will affect reproductive function in young adults; and (2) that immune system function will be altered in the heptachlor exposed group compared to controls. Secondary hypotheses are: (1) the biological indicators of reproductive and immune function will correlate with quantitative estimates of heptachlor exposure; and (2) there will be gender-specific changes in reproductive endocrine and immune function associated with the heptachlor exposure.

This study cohort consists of young adults who were exposed to heptachlor epoxide during a well-characterized episode in which the commercial milk supply on the Hawaiian island of Oahu was accidentally contaminated during a 15-month period (1981–1982). Contamination resulted in gestational and neonatal exposure to the children of women who drank cow's milk during that period. Characterization of exposure and adverse effect in this group has been conducted in three phases, the third of which is funded by the subject EPA STAR Grant. In the first phase, the investigators conducted two statewide population-based surveys to measure HE concentrations in human milk and sera. These surveys verified that HE concentrations in the biological specimens were significantly higher in the Oahu population than on the unexposed neighbor islands. Investigators also found a significant association between HE concentrations and reported cow's milk consumption during 1981 and 1982. In the second phase, an islandwide survey of 20,408 high school students was conducted to identify 1,891 young adults who were born during 1981 and 1982 and lived on Oahu for at least 15 years. Using this sampling frame, 332 Oahu-born participants and 113 participants not born on Oahu were selected to assess neurobehavioral function and academic achievement using standard test instruments and school records. Multivariate analyses controlling for confounding factors indicated that gestational exposure to HE was associated with lower neurobehavioral performance, especially abstract concept formation, visual perception, and motor planning, and with more reported behavioral problems. There were no significant associations between HE exposures and school-based performance measures, such as GPA.

The third phase investigation, funding under this grant, consists of a study of reproductive and immune function in young adults exposed to HE. The same sampling frame as Phase 2 is being used to recruit 400 Oahu-born young adults and 200 comparison participants who were not born on Oahu, matched by

## Grant Title and Principal Investigator

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Dean Baker – University of California - Irvine  
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## Key Findings

- This study is funding the third phase of an epidemiological study of a group of young adults exposed to heptachlor epoxide *in utero*. Reproductive and immunological function are being evaluated. Recruitment and data collection are ongoing
- Initial analysis of the reproductive and immune function studies in the subjects recruited thus far has found hormonal indications of slightly delayed sexual maturity indicators and shorter menstruation, correlated with the amount of heptachlor-contaminated milk ingested by the mothers.
- No differences in antibody levels, cytokine activity, or other immune factors measured have yet been found between exposed and control individuals.
- Study findings thus far have been limited by small sample size, incomplete followup, and lack of precise exposure data.

No peer reviewed articles have yet been published.

**Project Period: March 2003 to February 2007**

age and ethnicity. Indicators of reproductive function to be measured include serum testosterone in males, estradiol and progesterone in females, luteinizing hormone and follicle-stimulating hormone levels in both sexes, semen quality, and daily first morning urine sampling in females for one menstrual cycle to measure luteinizing hormone, estrone-3-glucuronide, and pregnanediol 3-alpha-glucuronide. Indicators of immune function being studied include skin tests for standard recall antigens, antibody titer response to immunization with tetanus and pneumococcal vaccine, Th1 and Th2 type CD4+ cell counts in peripheral blood, and susceptibility of peripheral blood T cells to activation-induced cell death using *in vitro* analysis of Fas (CD95) and its ligand (CD95L) expression. The analysis will compare outcomes between the Oahu-born and comparison groups, controlling for relevant confounders. Secondary comparisons among the Oahu-born population are being made based on individual estimates of gestational HE exposure.

### **Project Results and Implications**

This study has enrolled 250 participants, including 238 participants for whom data collection is substantially complete. Blood, urine, and semen samples from the 209 Oahu-born participants and the 29 control subjects are being examined for markers of reproductive and immune health. Preliminary analyses have found no strong associations between HE exposures and reproductive and immune function parameters, but slightly delayed sexual maturity and shorter menstruation appears to be weakly associated with the amount of maternal contaminated milk consumption. No differences have yet been found between exposed and control groups with regard to antibody levels, cytokine activity, or other immune factors. Thus, while preliminary data suggest anti-estrogenic effects of HE in the offspring of exposed mothers, the small sample size, limited followup, and lack of precise exposure data limit the study's conclusions thus far. Further data collection and analyses are ongoing to complete the analyses.

### **Relevance to ORD's Multi-Year Research Plan**

This project contributes to two of ORD's Multi-Year Plan long-term goals (LTG 1 and 2): (1) providing a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors, and (2) determining the extent of the impact of endocrine disruptors on humans, wildlife, and the environment. Specifically, the results may help characterize the dose-response curve for prenatal exposures to a suspected endocrine disruptor (heptachlor), help determine whether adverse developmental or reproductive effects are occurring in human populations following exposure to HE, and determine the extent to which exposure to endocrine disruptors contribute to the onset or increase in the severity of diseases.

### **Investigators**

Dean Baker – University of California - Irvine, California

### **For More Information**

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