

Relative Susceptibility of the Developing and Maternal Immune Systems to Immunosuppression by Dexamethasone

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The immune system of children is not fully developed until puberty, and prior to maturation the immune system varies in its susceptibility to chemical exposure. Furthermore, gestation constitutes a period of hormone-driven maternal immunosuppression that not only prevents rejection of the histoincompatible fetus as a foreign tissue allograft, but also increases maternal susceptibility to infections. Experiments in laboratory animals and limited human epidemiologic data suggest that immune system development and maturation constitute periods of greater sensitivity or susceptibility to immunosuppressive chemicals and certain drugs. Sensitivity may be expressed as suppression of function at lower doses than those that cause the same response in adults, or prolonged suppression of immune function compared to adults. A limited number of studies also suggest that susceptibility to immunotoxicants may be expressed as immunosuppression that occurs only following developmental exposure to chemicals or drugs that do not suppress function in adults exposed to the same agent. As part of this project, susceptibility of the developing immune system will be evaluated by exposing dams to the organochlorine pesticide heptachlor, and evaluating markers of innate and adaptive immune function in male and female offspring. A variety of developmental immunotoxicity animal testing protocols have been proposed (although none have been adopted), including those that would evaluate function in newborn offspring of exposed dams. However, immune system immaturity is typically cited as a reason to avoid early life testing of animals. This issue will be addressed as part of the current project by evaluating responses to standard tests of cellular and humoral immunity at three, four and a half, and six weeks of age, to estimate when responses follow typical adult patterns. Because traditional developmental immunotoxicity studies only evaluate immune function in offspring, these studies do not address potential additive or synergistic effects of immunotoxicants on the constitutively suppressed maternal immune system. Thus, the goal of this phase of the project is to investigate the relative sensitivity of immune function in the developing fetus and dam following gestational exposure to the well characterized immunosuppressive drug dexamethasone. Cellular and humoral immune function will be evaluated in offspring when they reach adult levels of immune function (i.e., at six weeks of age), and persistence of effects will be addressed by assays conducted at 14 and 28 weeks of age. (This abstract does not reflect U.S. EPA policy.)

Implications: The greater sensitivity and susceptibility of the developing immune system to immunotoxicants has been the subject of many reviews. However, only a handful of studies have evaluated the effects of xenobiotics on maternal immune function, or directly compared maternal and fetal immune system effects for dose sensitivity and persistence. Maternal hormone flux during gestation is important in maintaining pregnancy, in part due to suppression of immune function. Endocrine disrupting chemicals may therefore pose a threat to both mother and offspring, if exposure modulates the intensity or nature of homeostatic immune processes. In these studies, a determination that altered immune function is equally sensitive, and the effects equally persistent, in the fetus and dams will suggest that both maternal and developmental immunotoxicity should be considered in studies of developmental immunotoxicity.

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