Susceptibility of the Developing Immune System to Immunosuppressive Agents


This project evaluated three potentially immunosuppressive chemicals [dexamethasone (DEX), cyclosporin A (CYP-A), di-(2-ethylhexyl) phthalate—(DEHP)] for persistent immunotoxicity following in utero versus adult exposure of CD strain female rats. In addition to directly comparing age-related susceptibilities to immunotoxic insult, the study compared the utility of early (juvenile) versus late (adult) assessment of immunotoxicity following in utero exposure and the potential predictability of using cytokine biomarkers to reflect developmentally-induced functional immune changes. Pregnant and non-pregnant CD strain female rats were dosed with the test chemicals during a period of 16 consecutive days (corresponding in the pregnant females from gestation day 6 to 21). Female offspring from exposed dams were analysed for immune function including cytokine production capabilities at five weeks of age and early reproductive indices were also examined. Subsequent immune analysis was performed on offspring at 13 weeks of age including analysis of the non-pregnant exposed adults 13 weeks post exposure (for age-based comparisons). Results from the chemical exposures suggested that in utero exposed rats had increased sensitivity to DEX and CYP-A based on lower LOAEL values, increased severity of alterations, or greater persistence of alterations. For the third test chemical, DEHP, no overt immunotoxicity was detected in offspring exposed in utero or in adults following exposure. Some developmental effects (altered AGD) were noted. Hence, the current evaluation regime was able to compare age-related relative sensitivities to potential immunotoxicants and to discriminate among chemicals in terms of potential developmental immunotoxicity. No advantage was seen for adult vs. juvenile assessment following early exposure. In this study, cytokine biomarkers were frequently found to support functional differences but were not, by themselves, fully predictable of all immune alterations.

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