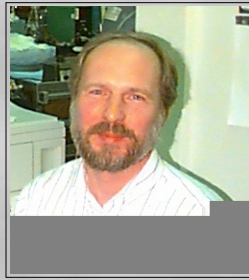


STUDIES OF THE ALTERATIONS IN ESTROGEN METABOLISM CAUSED BY EXPOSURE TO POLYCHLORINATED BIPHENYLS



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The main objective of this project is to determine the effects of polychlorinated biphenyl (PCB) exposure on phase I and phase II metabolism of 17 beta-estradiol (E2) in the liver and other tissues. The alteration of estrogen metabolism by PCB exposure is a mechanism by which xenobiotics may disrupt normal estrogenic signal transduction and cause alterations in fertility, fecundity, and neuroendocrine development. We hypothesize that in a congener-specific manner, PCBs will increase the rates of E2 hydroxylation and conjugation in liver and in estrogen target tissues. This aberrant estrogen metabolism can cause oxidative stress.

One aim of the project is to determine the effects of PCB (arochlors 1254 and 1260, and several individual congeners) exposure on the rates of cytochrome P450-catalyzed hydroxylation of E2. Female rats are treated with PCBs, and the levels of induced enzymes in microsomes prepared from liver and kidney are determined by the measurement of the cytochrome p450-catalyzed hydroxylation of E2. The effects of PCB exposure on E2 metabolism in human-derived breast, liver, kidney, and uterine cells in culture are also being investigated.

The next aim is to determine the effects of PCB exposure on phase II metabolism of E2 in liver and extrahepatic tissues. Estrogen glucuronosyltransferase, T3 and T4 glucuronosyl-transferase, and estrogen sulfotransferase activities are being determined by microsomes prepared from tissues of PCB-exposed female rats and from human-derived cells *in vitro*. It will be determined whether estrogens and the thyroid hormones, T3 and T4, are substrates for the same conjugating enzymes.

Another aim is to determine the effects of PCB exposure on the expression of cytochrome P450s of the CYP1A and the CYP1B gene subfamilies. RNA blots, immunoblots and the reverse transcriptase-polymerase chain reaction (PCR) are used to characterize gene expression in tissues of female rats and in human breast, kidney, and endometrial cells *in vitro*.

An additional aim is to determine the effects of PCB exposure and PCB-induced estrogen metabolism on oxidative stress in tissues of the female rat and in human breast cells *in vitro*. Lipid peroxides, DNA

strand breaks, and the presence of 8-hydroxyguanine in DNA are measured as evidence of oxidative stress. Oxidative stress can cause cytotoxicity, chromosomal aberrations, mutagenesis, age related cellular degeneration, and carcinogenesis.

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We welcome your comments and inquiries regarding this research project. Please forward comments to: Dr. David C. Spink, University at Albany, Wadsworth Center, NYS Dept. of Health, Empire State Plaza, PO Box 509, Albany, NY 12201-0509 david.spink@wadsworth.org

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