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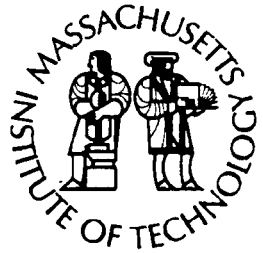

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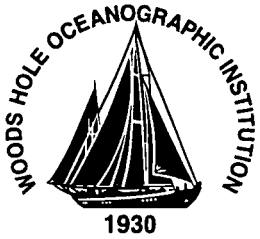

DOCTORAL DISSERTATION

Tetrachlorobiphenyl Metabolism, Toxicity, and Regulation of Cytochrome P450 Expression in a Marine Teleost Fish

by

Renee Devorah White

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TETRACHLOROBIPHENYL METABOLISM, TOXICITY, AND REGULATION OF CYTOCHROME P450 EXPRESSION IN A MARINE TELEOST FISH

by

Renee Devorah White

submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

ABSTRACT

The effects of 3,3',4,4'-tetrachlorobiphenyl (TCB) were examined in the marine fish scup (*Stenotomus chrysops*), focusing on the interactions between TCB and the CYP1A1 enzyme system. A low TCB dose (0.1 mg/kg) elicited strong and sustained induction of hepatic CYP1A1 mRNA, protein content, and catalytic activity. A high TCB dose (5.0 mg/kg) elicited similar, strong induction of hepatic CYP1A1 mRNA, but not of CYP1A1 protein content or catalytic activity. This post-transcriptional "suppression" at the high TCB dose was specific for CYP1A1, and was not seen with other hepatic enzymes. *In vitro* studies indicate that hepatic microsomal CYP1A1 is inactivated in the presence of TCB plus cofactor, likely due to the production of reactive oxygen species during TCB occupation of the active site. CYP1A1 inactivation by TCB *in vitro* may explain the TCB-elicited suppression of CYP1A1 protein content *in vivo*.

Both TCB doses elicited strong CYP1A1 induction in vascular endothelium of all organs, which was sustained for several weeks. Induction in intestinal epithelia was stronger at the high TCB dose, but induction in epithelia of liver, kidney, and gill were stronger at the low TCB dose. Both TCB doses caused proliferation of endoplasmic reticulum in liver, renal tubule necrosis, depletion of hematopoietic tissue in kidney, hyperplasia of gill epithelia, and increased number of melanomacrophage aggregates in spleen. The high dose induced tail fin erosion, affecting both epithelial and calcified bone tissue. Tissue alterations were more severe at the high TCB dose, and repair of lesions occurred by day 16 at the low dose. The high dose caused mortality of many individuals.

The two TCB congeners 3,3',4,4'-TCB and 2,2',5,5'-TCB were each converted to aqueous-soluble metabolites by hepatic microsomes from scup, beluga whale, and pilot whale. Induction response, correlation analysis, and inhibition studies indicate that 3,3',4,4'-TCB is metabolized by scup CYP1A1, and 2,2',5,5'-TCB by the putative scup CYP2B. Correlation analysis and inhibition studies suggest that 3,3',4,4'-TCB is metabolized by cetacean CYP1A. Both cetacean species expressed microsomal proteins that are immunochemically related to mammalian CYP2B forms. Cytochrome P450 systems from both cetacean species are partially characterized here.

Thesis Supervisor: John J. Stegeman, Senior Scientist, WHOI