

PROPERTIES OF POLYCHLOROBIPHENYLS AS SUBSTRATES AND INHIBITORS OF UDP-GLUCURONOSYLTRANSFERASE (UGT).

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Polychlorobiphenyls (OH-PCBs) are potentially toxic metabolites of the ubiquitous environmental pollutants, the PCBs. One mechanism of toxicity is endocrine disruption: OH-PCBs are weak estrogens and potent inhibitors of the sulfonation of estradiol and thyroid hormones. Certain OH-PCBs were shown to inhibit the sulfonation and glucuronidation of a major metabolite of the polycyclic aromatic hydrocarbon, benzo(a)pyrene (BaP), 3-hydroxy-benzo(a)pyrene (3-OH-BaP) in fish intestine (van den Hurk and James, 2002). This suggested another mechanism of toxicity, interference with phase II detoxification of hydroxylated xenobiotics. PCBs accumulate in fish, in part because they are metabolized more slowly in fish than in humans. Small amounts of OH-PCBs have been found in tissues of fish exposed to PCBs. Thus, people who eat fish from heavily PCB-contaminated waters will be exposed to PCBs and OH-PCBs. The OH-PCBs are expected to be substrates for glucuronidation and sulfonation, however there is little information on these pathways in fish or humans. We examined the properties of selected para-OH-PCBs with varying numbers of chlorine substituents as substrates for UGT in intestinal and hepatic microsomes from the channel catfish, *Ictalurus punctatus*. The effect of a mixture of OH-PCBs shown to inhibit glucuronidation on the biotransformation and DNA-binding of a proximate carcinogenic metabolite of benzo(a)pyrene, (-)-benzo(a)pyrene-7,8-dihydrodiol (BaP-7,8-D), was studied in an isolated perfused catfish liver. The rate of glucuronidation of the OH-PCBs varied with substrate, but enzyme efficiency (V_{max}/K_m) was consistently 3-fold to 10-fold higher for intestine, compared with liver. For a series of para OH-PCBs with Cl atoms flanking the OH group, K_m values ranged from 0.05 to 0.48 mM for intestine and 0.16 to 0.67 mM for liver. V_{max} values ranged from 95 to 800 pmole/min/mg protein in intestine to 45 to 170 pmole/min/mg protein in liver. At substrate concentrations of 10 μ M, which were somewhat higher than the environmentally relevant range, rates were typically <5 pmole.min⁻¹.mg⁻¹ for liver microsomes and between 11 and 22 pmole/min/mg protein for intestinal microsomes. Infusion of a mixture of OH-PCBs into isolated perfused catfish livers prior to infusion of [3H]-BaP-7,8-D resulted in a 5-fold increase in formation of DNA adducts and reduced formation of glucuronides of BaP-7,8-D. These results show that OH-PCBs are low affinity substrates for UDP-glucuronosyltransferase, especially in liver, and suggest that at environmentally relevant concentrations, this pathway will be operating under sub-optimal conditions. The results further suggest that co-exposure of animals to PCBs and PAH may result in increased toxicity of the PAH. The authors wish to acknowledge Drs. Larry W. Robertson and Hans-Joachim Lehmler for supplying some of the OH-PCBs used in these studies. This work was supported by 1-P42-ES-07375.