

2,2',4,4',5,5'-Hexachlorobiphenyl as a 2,3,7,8-Tetrachlorodibenzo-p-dioxin Antagonist in C57BL/6J Mice

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2,2',4,4',5,5'-Hexachlorobiphenyl as a 2,3,7,8-Tetrachlorodibenzo-p-dioxin Antagonist in C57BL/6J Mice. BIEGEL, L., HARRIS, M., DAVIS, D., ROSENGREN, R., SAFE, L., AND SAFE, S. (1989). *Toxicol. Appl. Pharmacol.* 97, 561-571. At doses as high as 750 to 1000 pmol/kg, 2,2',4,4',5,5'-hexachlorobiphenyl (HCBP) did not cause fetal cleft palate, suppress the splenic plaque-forming cell response to sheep red blood cells, or induce hepatic microsomal ethoxyresorufin O-deethylase (EROD) in C57BL/6J mice. Despite the lack of activity of HCBP in eliciting any of these aryl hydrocarbon (Ah) receptor-mediated responses, competitive binding studies indicated that HCBP competitively displaced 2,3,7,8-[³H]tetrachlorodibenzo-p-dioxin (TCDD) from the murine hepatic cytosolic receptor. Cotreatment of C57BL/6J mice with TCDD (3.7 nmol/kg) and HCBP or 4,4'-diiodo-2,2',5,5'-tetrachlorobiphenyl (12-TCBP) (400 or 1000 pmol/kg) showed that both compounds partially antagonized TCDD-mediated cleft palate and immunotoxicity (i.e., suppression of the splenic plaque-forming cell response to sheep red blood cells), and HCBP antagonized TCDD-mediated hepatic microsomal EROD induction. Thus, HCBP and 12-TCBP, like the commercial polychlorinated biphenyl mixture Aroclor 1254, were partial antagonists of TCDD action in C57BL/6J mice; however, it was also apparent from the results that Aroclor 1254 was the more effective antagonist at lower doses. Using [³H]TCDD, it was also shown that some of the effects of HCBP on TCDD-mediated cleft palate may be due to the decreased levels of TCDD found in the fetal palates after cotreatment with TCDD and HCBP. 4,4'-[¹²⁵I]diiodo-2,2',5,5'-tetrachlorobiphenyl ([¹²⁵I]TCBP) of high specific activity (3350 Ci/mmol) was synthesized and used to investigate the direct binding of this compound to the murine hepatic Ah receptor or other cytosolic proteins. No direct specific binding was observed between [¹²⁵I]TCBP and any cytosolic proteins using a sucrose density gradient assay procedure. These results contrasted with previous studies with Aroclor 1254 that suggested that this mixture acted as a competitive Ah receptor antagonist.