2,2',4,4',5,5'-Hexachlorobiphenyl as an Antagonist of the Teratogenicity of 3,3',4,4',5-Petachlorobiphenyl in C57BL/6 mice

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1. Introduction

Polychlorinated biphenyls (PCBs) are hazardous environmental chemicals that are frequently detected as residues in animals and humans. Commercial PCBs elicit a broad spectrum of biochemical and toxic responses that include body weight loss, porphyria, hepatotoxicity, reproductive and developmental toxicity, immunotoxicity, carcinogenicity and the induction of hepatic phase I and II drug metabolizing enzymes[1]. Many of the effects caused by the commercial PCBs resemble those responses observed after treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related toxic halogenated aromatic hydrocarbons. The most toxic PCB congeners[2], namely 3,3',4,4'-tetrachlorobiphenyl, 3,3',4,4',5-pentachlorobiphenyl (PeCB) and 3,3',4,4',5,5'-hexachlorobiphenyl are approximate isostereomers of TCDD in their coplanar conformations and elicit similar biochemical and toxic responses. There is information which suggests that PeCB may be the most toxic coplanar PCB congener. Recent studies in our laboratory have demonstrated the teratogenic effects of PeCB in C57BL/6 mice (i.e., induction of cleft palate and hydronephrosis) with a TEF (toxic equivalency factor) ranging from < 0.07 to 0.04[1]. Earlier studies reported that the commercial PCB mixture, Aroclor 1254[3], and one diortho coplanar PCB analog, 2,2',4,4',5,5'-hexachlorobiphenyl (HeCB)[4], partially antagonized TCDD-induced teratogenicity (fetal cleft palate) in C57BL/6 mice.

2. Objectives

The objective of this study was to determine the abililty of HeCB to antagonize the teratogenicity of PeCB in C57BL/6 mice.

3. Methods

Mature male and virgin female C57BL/6 mice were purchased from Harlan, Sprague-Dawley Inc., Houston, TX and maintained on feed (Teklad Premier Laboratory Diet, Madison, WI) and

water *ad libitum* at the Texas A&M University Laboratory Animal Resources and Research Facility. Animals were housed in a temperature-controlled and artificially illuminated room (12-h light cycle) free from any known sources of chemical contamination. After an acclimation period of 1 wk, females were mated with mature males of the same strain and source in polycarbonate cages. Successful mating was determined by the presence of vaginal copulatory plugs on the next morning and was considered as day 0 of pregnancy. Pregnancies were confirmed by measuring the maternal weight gain. Pregnant animals were administered on day 10 a single oral dose of PeCB dissolved in corn oil at concentrations ranging from 0 to 2088 μg/kg body weight either alone or in combination with 271 mg HeCB/kg body weight. All dosing volumes were 10 ml/kg body weight. Control animals were either treated with HeCB (271 mg/kg), corn oil or left untreated. Body weights and general appearance of pregnant mice were monitored daily. Dams were euthanized by carbon dioxide asphyxiation on day 17 of gestation. The litter and liver weights were recorded. The uterine horns were opened and number of implants, resorptions, and live fetuses were counted. Live individual fetuses were removed from the uterus, blotted dry, weighed and examined for gross malformations. The fetuses were fixed in Bouin's solution for at least one wk and examined for cleft palate and hydronephrosis. All data were subjected to analysis of variance using the General Linear Models Procedure of the Statistical Analysis System, SAS Institute, Inc., 1982[5]. The significance of the differences among treatment groups with variable means was determined by Tukey's Studentized Range Test. All statements of significance were at a probability level of $P \leq 0.05$ level.

4. Results

There was no apparent signs of maternal toxicity in any of the treatment groups, except in the group treated with the highest dose of PeCB plus HeCB (data not shown). PeCB alone induced a dose-dependent increase in the number of fetuses with cleft palate, ranging from 21 to 100 % (Figure 1). All fetuses had cleft palate from dams treated with the highest dose of PeCB (2088 μg/kg body weight). Cotreatment of the dams with PeCB (522, 783, 1044 or 2088 μg/kg body weight) plus HeCB (271 mg/kg body weight) significantly reduced the number of fetuses with cleft palate in all treatment groups, except in the group of animals treated with 2088 μg PeCB/kg body weight.

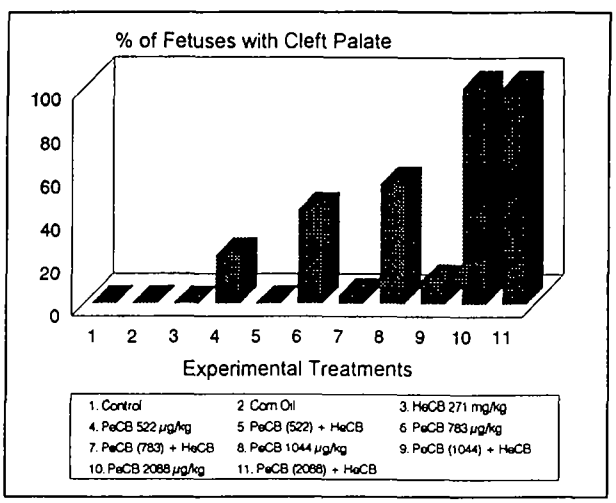

Figure 1. Induction of fetal cleft palate in C57BL/6 mice by PeCB: Antagonism by 2,2',4,4',5,5'-HeCB.

PeCB alone at a dose of 1044 μg/kg body weight produced 64% of fetuses with cleft palate; whereas, the same dose plus HeCB (271 mg/kg body weight) resulted in only 13% of fetuses with cleft palate. Pregnant mice treated with 783 or 522 μg PeCB/kg body weight resulted in 45% and 21% of fetuses with cleft palate, respectively. Cotreatment of dams with a dose of 783 μg PeCB/kg plus 271 mg HeCB/kg produced only 4% of fetuses with cleft palate, and none of the fetuses had cleft palate in the animals treated with 522 μg PeCB/kg in combination with HeCB. At a concentration of 271 mg HeCB/kg, no significant increase in the incidences of either cleft palate or hydronephrosis were observed, and this dose of HeCB did not antagonize the PeCB-induced hydronephrosis in any of the treatment groups. The results from this study clearly demonstrate that HeCB acts to partially antagonize the teratogenicity (induction of fetal cleft palate) of PeCB in C57BL/6 mice.

5. References

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