Bull. Environ. Contam. Toxicol. (1984) 33:78–83

Bulletin of Environmental Contamination and Toxicology

Hypercholesterolemia Induced by Dietary PCBs (Aroclor 1254) in Fischer Rats

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An increase in hepatic and serum cholesterol in PCB-treated rats was first reported in 1971 (Nagai et al.). This observation was confirmed in subsequent studies by several Japanese investigators (Kiriyama et al. 1974; Kato et al. 1978; Innami et al. 1978; Kato and Yoshida 1980).

In addition, one of the lipoprotein fractions of serum cholesterol has been reported as being elevated in PCB-treated animals. Serum high density lipoprotein-cholesterol (HDL-cholesterol) was increased for 60 days in rats given one 40 mg/kg intraperitoneal injection of Aroclor 1254 (Ishikawa et al. 1978). Rats fed diets containing 30% protein (casein) and 1000 PPM Aroclor 1248 for 24 days exhibited elevated serum cholesterol (217% increase) and elevated HDL-cholesterol (254% increase) (Kato et al. 1982).

In most of the above cited studies relatively large doses of PCBs were administered for lengthy periods of time. The objectives of the present study were to produce hypercholesterolemia and hyperlipoproteinemia (HDL-cholesterol) in a minimum amount of time using minimally toxic dietary PCB concentrations which would not adversely affect food consumption or body weight gain in juvenile male Fischer rats.

MATERIALS AND METHODS

Male Fischer rats 28 days old (Charles River COBS/CDF) were divided into six groups of eight animals each. The rats were individually housed in wire-bottom cages with food and deionized water available ad libitum, and acclimated to controlled lighting (from 0700 to 1900) and temperature (26°C ± 2°C) for 10 days. All groups were fed diets (Table 1) that contained the following concentrations of PCBs: 0, 2, 4, 8, 16, or 32PPM Aroclor 1254. The rats were assigned according to a randomized block design and fed the diets described above for four days. Food intakes and body weight gains were recorded at the end of the study. The animals were sacrificed with diethyl ether anesthesia. Blood samples were obtained from the abdominal aorta and analyzed for serum cholesterol and HDL-cholesterol (Allain et al. 1974). The liver was removed and its wet weight determined. Results were analyzed by one-way analysis

Table 1. Composition of Diet

Constituents	% in Diet
[1]Vitamin Mix (A.I.N. Vitamin Mix 76)	1.00
[2]Alpahcel (Non-nutritive Bulk)	5.72
[3]Salt (A.I.N. Mineral Mix 76)	3.50
[4]Cornstarch	57.00
[5]Vitamin-Free Casein	25.00
[6]Choline Chloride	0.20
[7]d,l-Methionine	0.08
Fat (Mazola Corn Oil)	7.50

[1-7]I.C.N. Nutritional Biochemicals, Cleveland, Ohio 44128

of variance with multiple comparisons of group means for statistical significance using Duncan's New Multiple Range test.

RESULTS AND DISCUSSION

The total food consumption, body weight gain and final body weight data are presented in Table 2. There were no significant differences among the PCB-treated groups and the control group for any of these three variables.

Table 2. Effects of Dietary PCBs (Aroclor 1254) on Final Body Weight, Body Weight Gain and Total Food Intake

	Dietary PCB Concentration (PPM)*					
	0	2	4	8	16	32
Final Body Wt. (G)	118 ± 4^{ab}	110 ± 2^{a}	113 ± 5^{ab}	125 ± 2^{b}	120 ± 3^{ab}	116 ± 5^{ab}
Body Wt. Gain (G)	18 ± 1^{ab}	15 ± 1^{a}	17 ± 1^{ab}	19 ± 1^{b}	16 ± 1^{ab}	17 ± 1^{ab}
Total Food Intake (G)	51 ± 2^{ab}	47 ± 1^{a}	48 ± 2^{a}	56 ± 2^{b}	52 ± 1^{ab}	52 ± 2^{ab}

*Mean ± S.E. of 8 rats per group. Values in the same row not sharing a common superscript are significantly different ($p < 0.05$).

Relative wet liver weights were significantly elevated in those groups consuming diets containing 16 and 32PPM Aroclor 1254. These data are illustrated in Figure 1.

Serum cholesterol values seen in Figure 2 appear to mimic a pattern demonstrated by the relative wet liver weight data. However, serum cholesterol was significantly elevated not only in the groups which consumed 16 and 32PPM Aroclor 1254 but also in the group which consumed 8PPM Aroclor 1254.

Although the serum HDL-cholesterol values for all the PCB-treated groups were higher than the control group, only the rats consuming 32PPM Aroclor 1254 exhibited significantly elevated values

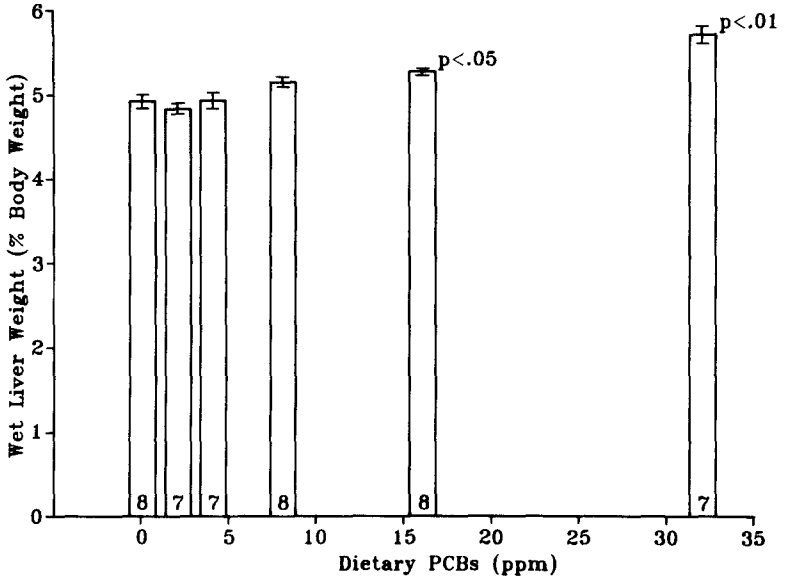

Figure 1. Effect of dietary PCBs (Aroclor 1254) on wet liver weight (mean +/- S.E.). Numbers in bars represent the number of specimens per group. Means different than the control group are indicated by p-values.

(Figure 3). This phenomenon can in part be explained by the observation that the variability of the serum HDL-cholesterol values is approximately three times greater than that for serum

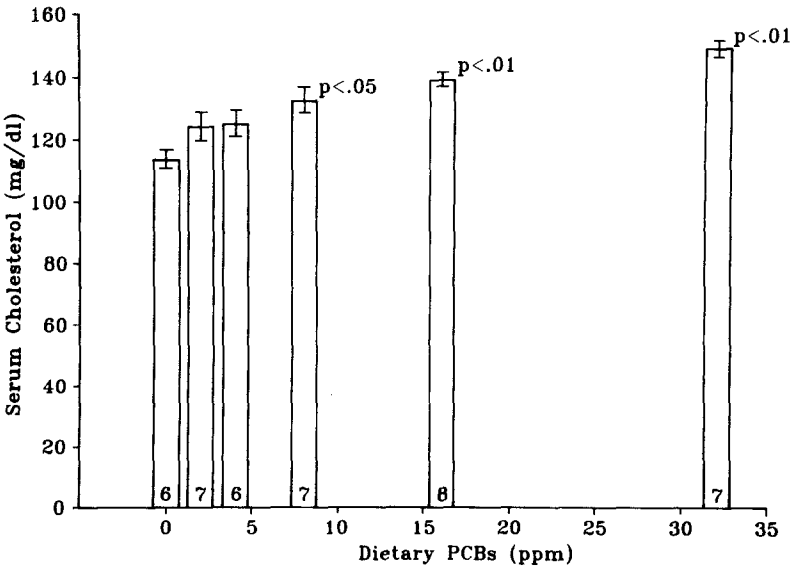

Figure 2. Effect of dietary PCBs (Aroclor 1254) on serum cholesterol (mean +/- S.E.). Numbers in bars represent the number of specimens per group. Means different than the control group are indicated by p-values.

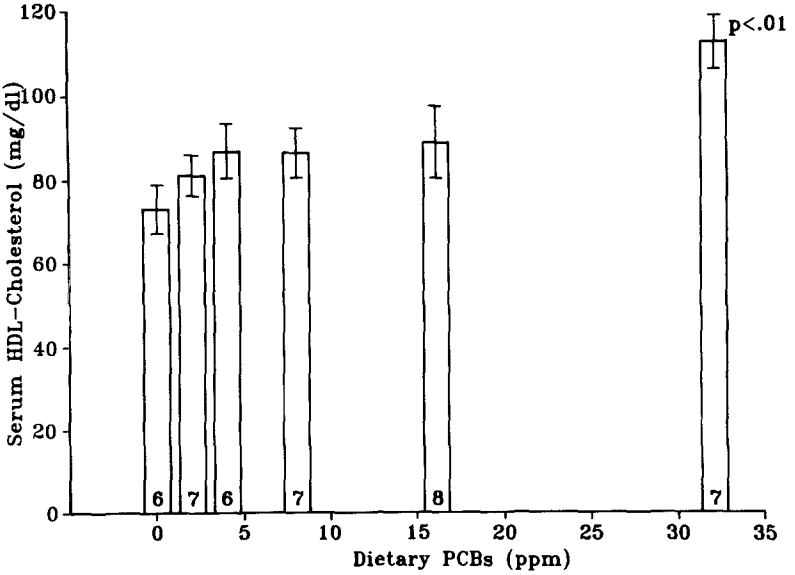

Figure 3. Effect of dietary PCBs (Aroclor 1254) on serum HDL-cholesterol (mean +/-S.E.). Numbers in bars represent the number of specimens per group. Means different than the control group are indicated by p-values.

cholesterol (mean coefficient of variation for all groups is 6.97 for serum cholesterol versus 18.39 for serum HDL-cholesterol). Linear regression analysis of the data described above is found in Table 3. There were no significant correlations between dietary PCB concentration and final body weight, body weight gain or total food intake. There were significant correlation coefficients for dietary PCB concentration versus relative wet liver weight, serum cholesterol and serum HDL-cholesterol. These significant r-values agreed with the data illustrated in Figures 1, 2, and 3.

In evaluating the induction of hypercholesterolemia by dietary PCBs in this investigation several important questions must be considered. Is the duration of the study long enough to produce alterations in liver structure and function? Is the highest dietary PCB concentration sufficient to adversely affect liver structure and function without decreasing food consumption and body weight? Is the lowest dietary PCB concentration inadequate to induce hypercholesterolemia? These questions will be addressed in the following paragraphs.

Two aims of the present study were to elicit hypercholesterolemia in a minimum amount of time using a minimally toxic dietary PCB concentration. If these two criteria were satisfied, then it would be less likely that any significant decreases would be observed in total food consumption and body weight gain. In a recent article the onset of hepatomegaly in PCB-treated Fischer

Table 3. Linear Regression Analysis

Variable	Y-Intercept	Slope	r	p-value
Final Body Wt.[a]	114.98	0.11	0.10	N.S.
Body Wt. Gain[b]	17.08	-0.02	-0.08	N.S.
Total Food Intake[a]	48.90	0.06	0.08	N.S.
Rel. Wet Liver Wt.[c]	4.87	0.03	0.80	<0.001
Serum Cholesterol[d]	123.56	0.88	0.61	<0.001
Serum HDL-Cholesterol[d]	78.54	0.99	0.54	<0.001

[a] $N = 48$, [b] $N = 46$, [c] $N = 47$, [d] $N = 42$

rats was reported to be four days when the animals were fed a diet containing 20PPM Aroclor 1254 (Carter, 1983). Four days of dietary treatment were chosen for this study. As can be seen in Figure 2, this exposure time to dietary PCBs was adequate to cause hypercholesterolemia. Therefore, the first question asked in the preceding paragraph has an affirmative answer.

The dietary PCB concentrations used were selected after consideration of the following data: (1) dietary PCB concentrations greater than 179PPM Aroclor 1254 cause reduction in food consumption and depress body weight gain in weanling male Fischer rats (Carter and Mercer, 1983) and (2) dietary PCB concentrations greater than 10 and less than 20PPM Aroclor 1254 represent minimally toxic doses for the induction of hepatomegaly in weanling male Fischer rats (Carter, unpublished data). The dietary PCB concentrations used in this study had no adverse effects on food consumption and body weight (Table 2) and were adequate to produce hepatomegaly in those animals receiving the two highest dietary concentrations of 16 and 32PPM Aroclor 1254 (Figure 1 and Table 3). Therefore, the second and third questions raised earlier have been satisfactorily answered.

The hypercholesterolemia reported in this investigation can be partly accounted for by the significant increase in serum HDL-cholesterol. However, a more complete accounting would require evaluation of serum low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol. These parameters will be assessed in a subsequent study.

Acknowledgments. This research was supported by an award from the Oral Roberts University School of Medicine Intramural Research Grant Program. I would like to recognize the important technical contribution made by Ms. Terry Diamond, and give special thanks to Ms. Arlene Dewell for typing this manuscript.

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Received February 14, 1984; accepted March 6, 1984.