Reproductin and Teratology Studies with Three Polychlorinated Biphenyls in Albino Rats

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Running Title: Reproductive Studies with 3 PCB's in Albino Rats.

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DSW 035652

STLCOPCB4019478

ABSTRACT

Reproduction and Teratology Studies with Three Polychlorinated Biphenyls in Albino Rats. Fancher, Otis E., Keplinger, M. L., Plank, J. B., Wheeler, E. P., and Calandra, J. C. (0000). Toxicol. Appl. Pharmacol. 00, 00 - 00. Three generation reproduction studies and teratology studies were conducted with 3 polychlorinated biphenyls (Aroclors 1242, 1254 and 1260) in albino rats. Aroclor 1242 at a dietary level of 100 ppm adversely affected mating and incidence of pregnancy during the second generation. Except for a suggestion of some decrease in the inclination to mate among other groups fed 10 or 100 ppm of the test materials during the second and third generations, no other reproductive parameter was affected. None of the materials was judged to be teratogenic at dosage levels of 10 and 30 mg/kg.

STLCOPCB4019479

INDEX TERMS

Aroclors

Aroclor 1242

Aroclor 1254

Aroclor 1260

Polychlorinated Biphenyls

Reproductive effects of, in albino rats

Teratology study of, in albino rats

DSW 035654

STLCOPCB4019480

Reproduction and Teratology Studies with Three Polychlorinated Biphenyls[1] in Albino Rats

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Background toxicological information has been summarized by Fancher et al. (0000) in the introductory paper of this series. Because of the demonstrated reproductive effects of polychlorinated

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biphenyls in various avian species and in view of the reported occurrence of weak deformities in chicks hatched from eggs treated with Aroclor 1242, the present study was conducted for assessment of reproductive and teratogenic effects of 3 Aroclors in a standard mammalian species.

METHODS

A. 3-Generation Reproduction Study

The animals employed were weanling albino rats of the Charles River strain(Charles River Breeding Laboratories, North Wilmington, Mass.). A control group and 9 treatment groups, each consisting of 8 male and 16 female animals, were employed, 3 treatment groups for each of the 3 Aroclors studied.

All diets were prepared fresh each week by mixing the appropriate Aroclor at levels of 1, 10 and 100 ppm with a standard pulverized stock ration(Special Mix Mouse Chow, Ralston Purina Company, St. Louis, Missouri). The control animals were fed the basic ration alone. Both food and water were available ad libitum. Except during mating trials, each animal was individually housed. All parental animals in all groups were maintained on the appropriate diets without interruption until sacrifice which followed weaning of the Fb (second) litters.

Initially the body weight of each parental animal was determined and all animals were weighed weekly until mating trials began. No further weights were determined except for terminal weights just

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prior to sacrifice. Parental animals were observed daily for mortality and behavioral reactions.

Mating trials were initiated with each generation when the animals were 100 days old. The 16 females in each group were caged in pairs and mated with a male randomly selected from within the same group. Daily observations for evidence of copulation (copulatory plug or vaginal blood) were made and the male was removed if, during the next estrous cycle of five days, no further signs of mating were observed. Any male failing to mate within ten days was replaced by another male from the same group. Females were permitted access to a maximum of 3 males. Mating Indices and Fertility Indicies were calculated.

All pups at birth were examined for gross physical abnormalities and the numbers of viable and stillborn pups of each litter were recorded. Records of survival at designated intervals during the lactation period were maintained and litters of more than 10 pups were reduced to that number by random sacrifice on the fifth day of the lactation period. Lactation, Live Birth and Survival Indices were calculated. A final examination for physical abnormalities was made at weaning. The Fa (first) litters were weaned 21 days postpartum and the parental females were again mated after 10 days to obtain Fb(second) litters. Eight males and 16 females from the Fb progeny of each group were selected at weaning for use as parental animals for the next generation.

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A gross autopsy was performed on any parental animal which died during the study and tissues were preserved for microscopic examination when feasible. After weaning of the Fb litters, parental animals were sacrificed after determination of final body weights. All males and 8 females from each group were subjected to gross pathologic examination. The weights of the liver, kidneys, spleen, gonads, heart and brain were recorded and organ to body weight and organ to brain weight ratios were calculated.

Microscopic pathologic studies were conducted on tissues from five male and five female parental animals from the control group and from each high treatment level group except for the F2 parents treated with Aroclor 1242. In this case tissues from parental animals treated at the intermediate level were examined.

B. Teratology Study - Albino Rats

The animals employed were female Charles River albino rats bred at the Charles River Breeding Laboratories, North Wilmington, Mass. These were confirmed pregnant by sperm-positive results of vaginal examination and were shipped on Day One of gestation, Day Zero being the day of insemination.

A control group and 6 treatment groups (treatment levels of 10 and 30 mg/kg/day for each of the Aroclors) were employed, each consisting of 26 animals. The test materials were administered orally as solutions in corn oil using a hypodermic syringe equipped with a ball-tipped intubation needle. Solutions were prepared daily

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in concentrations such that all animals received equivalent quantities of corn oil on a mg/kg basis. Control animals were treated with corn oil alone. All animals were treated once daily from the sixth through the fifteenth day of gestation (10 doses). Food and water were available ad libitum.

All animals were weighed daily during the dosing period and just prior to sacrifice. Daily records of mortality and reactions were maintained.

All females were sacrificed by carbon dioxide asphyxiation on the 20th day of gestation. An incision was made in the abdominal wall and the full extent of both uterine horns was exposed. Fetal swellings, implantation sites and corpora lutea were counted, special attention being paid to resorption sites or any other uterine abnormalities.

The number of viable fetuses present in the uterus was determined, spontaneous movement and a more ruddy color distinguishing live from dead animals. Each fetus was removed by placing a small hemostat on the umbilical cord, flush with the abdominal wall, and cutting the cord distal to the clamp. Blotting paper was used to remove excess amniotic fluid and blood prior to weighing the animals.

External examinations were made for detection of abnormalities which might include hydrocephaly, exencephaly, meningoencephalocele, simple meningocele, anophthalmia, microphthalmia, cleft lip, mandible or palate, oblique facial cleft, micrognathia, external ear abnormalities in size, shape or position, unusual size or position of

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the limbs, number and disposition of the digits, umbilical hernia, gastroschisis, myelomeningocele, spina bifida and scoliosis.

Two-thirds of the fetuses from each litter were examined for skeletal development using the alizirin red staining technique described by Hurley (1965). Internal development of the remaining fetuses was evaluated using the free-hand razor blade sectioning technique of Wilson and Warkany (1965).

RESULTS

Statistical treatment of all data analyzed consisted of Analysis of Variance followed by application of "t"-tests to any significant disclosures.

A. 3-Generation Reproduction Study

No effect on body weights of either parental animals or weanlings was observed among any group of any generation. No behavioral reactions were observed and mortality was unaffected. Pathologic examination of the occasional animal which died during the study failed to reveal any relationship between ingestion of the Aroclors and the death of the animals.

No gross pathologic findings among parental animals could be related to the ingestion of test materials. Evaluation of organ weight and organ to body weight and organ to brain weight ratio data disclosed several randomly occurring intergroup differences. Only those effects related to the liver might be attributed to treatment with the Aroclors. There is an indication that the three materials at the level of 100 ppm

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may cause increased liver weights and increases in liver to body weights and/or liver to brain weight ratios. These effects, if they are real, were moderate in degree and inconsistent in pattern with respect to dose level, sex and generation. It has been shown in a chronic rat study (Fancher et al., (0000) that each of the Aroclors caused liver effects at a dietary level of 100 ppm, but the effects were delayed in development, being apparent at the 24-month, but not at the 12-month or earlier sacrifices. In the present study the animals were treated for approximately 6 months only.

No changes which could be correlated with treatment were observed among tissues from sacrificed parental animals. Findings for treated animals were essentially the same as those for control animals. Focal epithelial hyperplasia of the bladder was noted among some F2 animals; one control female, one male treated with Aroclor 1242 at 10 ppm, one male and 2 females (from the same litter) treated with Aroclor 1254 at 100 ppm, and one female treated with Aroclor 1260 at 100 ppm. This hyperplasia was associated with focal cystitis and, in some cases, with mineralized calculi.

Mating indicies were somewhat decreased by all three materials at levels of 10 and 100 ppm, particularly during the second and third generations, being most evident with Aroclor 1242 at the 100 ppm level. In this case also the incidence of pregnancy was low and since only two females produced F2b litters, it was not possible to continue this level through the third generation. Data for reproduction perform-

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ance are presented in Table 1.

The number of live pups per litter born was not affected for any treatment group, and all pups delivered appeared normal. Erratic variations were observed in the number of pups weaned per litter but no consistent compound or dose correlation was apparent. Weanling body weights were normal for all groups and gross examination at weaning disclosed no external abnormalities. Survival data are presented in Table 2.

B. Teratology Study

Maternal body weights and weight gains were slightly decreased by treatment with Aroclors 1254 and 1260. These data are given in Table 3. No dose-effect correlation was apparent.

No deaths occurred among animals of any group and no abnormal reactions were noted.

The results of the sacrifice on Gestation Day 20 are presented in Table 4. Animals in all groups were free of gross uterine abnormalities. There is a suggestion that the Aroclors may exert some effect on the incidence of resorptions but the slight magnitude of any effect and the absence of any clear-cut dose correlation make this of doubtful significance. No other reproductive parameter was affected.

None of the materials at either level affected fetal body weights or sex ratios.

All fetuses appeared normal and were free of gross abnormal-

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ities. Data regarding fetal skeletal development are summarized in Table 5. None of the materials had an effect on skeletal development at either treatment level.

Examination of fetuses for internal development revealed atria of abnormal size among the progeny from all groups. The incidence of this abnormality did not differ significantly among the control and test groups. Twelve percent of the fetuses from dams treated with Aroclor 1254 at the dose level of 30 mg/kg had caudal renal ectopia. This abnormality was not seen among the progeny of any other group. Data with respect to fetal internal development are summarized in Table 6.

DISCUSSION

Aroclor 1242 at a dietary level of 100 ppm adversely affected mating and the incidence of pregnancy among albino rats during the second generation of a scheduled 3-generation study. Except for a suggestion of decreased inclination to mate among other groups fed 10 or 100 ppm of the test materials during the second and third generations and some erratic variations in pup survival to weaning age, no other reproductive parameter was affected.

None of the materials are judged to be teratogenic in albino rats at levels of 10 and 30 mg/kg. The non-occurrence of renal ectopia with 10 mg/kg of Aroclor 1254 or among the progeny of rats treated at either level with the closely related Aroclors makes it doubtful that this defect is a specific teratogenic response.

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TABLE 1

Reproductive Performance of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Dietary Level (ppm)	Litter	Mating Index		Incidence of Pregnancy		Fertility Index		Incidence of Parturition	
		Fraction	Percent	Fraction	Percent	Fraction	Percent	Fraction	Percent
None-Control	F1a	17/25	68.0	16/16	100	16/17	94.1	15/16	93.8
	F1b	15/20	75.0	15/15	100	15/15	100	15/15	100
	F2a	16/37	43.2	14/16	87.5	14/16	87.5	14/14	100
	F2b	14/26	53.8	14/14	100	14/14	100	14/14	100
	F3a	15/66	22.7	13/16	81.2	13/15	86.7	11/13	84.6
	F3b	12/16	75.0	12/12	100	12/12	100	11/12	91.7
Aroclor 1242 1	F1a	16/37	43.2	16/16	100	16/16	100	16/16	100
	F1b	15/21	71.4	15/15	100	15/16	93.8	15/15	100
	F2a	15/27	55.6	15/16	93.8	15/15	100	15/15	100
	F2b	15/18	83.3	14/15	93.3	14/15	93.3	14/14	100
	F3a	13/77	16.9	9/16	56.2	9/13	69.2	9/9	100
	F3b	9/23	39.1	8/9	88.8	8/9	88.9	8/8	100
10	F1a	16/43	37.2	16/16	100	16/16	100	15/16	93.8
	F1b	16/24	66.7	16/16	100	16/16	100	16/16	100
	F2a	13/53	24.5	12/16	75.0	12/13	92.3	12/12	100
	F2b	13/24	54.2	12/12	100	12/13	92.3	12/12	100
	F3a	16/43	37.2	16/16	100	16/16	100	15/16	93.8
	F3b	16/28	57.1	15/16	93.8	15/16	93.8	15/15	100
100	F1a	15/43	34.9	15/16	93.8	15/15	100	14/15	93.3
	F1b	15/24	62.5	15/15	100	15/15	100	15/15	100
	F2a	11/78	14.1	7/16	43.8	7/11	63.6	7/7	100
	F2b	2/37	5.4	2/7	28.6	2/2	100	2/2	100

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TABLE 1 (Continued)

Reproductive Performance of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Dietary Level (ppm)	Litter	Mating Index		Incidence of Pregnancy		Fertility Index		Incidence of Parturition	
		Fraction	Percent	Fraction	Percent	Fraction	Percent	Fraction	Percent
Aroclor 1254	F1a	16/29	55.2	16/16	100	16/16	100	16/16	100
1	F1b	16/29	55.2	16/16	100	16/16	100	15/16	93.8
	F2a	16/42	38.1	12/16	75.0	12/16	75.0	12/12	100
	F2b	11/28	39.3	11/12	91.7	11/11	100	11/11	100
	F3a	18/58	31.0	12/18	66.7	12/16	75.0	9/12	75.0
	F3b	14/24	58.3	11/14	78.6	11/12	91.7	11/11	100
10	F1a	16/23	69.6	16/16	100	16/16	100	16/16	100
	F1b	16/21	76.2	16/16	100	16/16	100	15/16	93.8
	F2a	14/63	22.2	11/16	68.8	11/14	78.6	10/11	90.9
	F2b	11/32	34.4	10/11	90.9	10/11	90.9	9/10	90.0
	F3a	16/54	29.6	14/16	87.5	14/16	87.5	12/14	85.7
	F3b	14/35	40.0	13/14	92.9	13/14	92.9	13/13	100
100	F1a	16/28	57.1	16/16	100	16/16	100	15/16	93.8
	F1b	16/26	61.5	16/16	100	16/16	100	13/16	81.3
	F2a	14/73	18.2	13/16	81.2	13/14	92.9	13/13	100
	F2b	10/52	19.2	9/13	69.2	9/10	90.0	9/9	100
	F3a	11/36	30.6	11/11	100	11/11	100	10/11	90.9
	F3b	8/31	25.8	8/8	100	8/8	100	8/8	100

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TABLE 1 (Continued)

Reproductive Performance of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Dietary Level (ppm)	Litter	Mating Index		Incidence of Pregnancy		Fertility Index		Incidence of Parturition	
		Fraction	Percent	Fraction	Percent	Fraction	Percent	Fraction	Percent
Aroclor 1260 1	F1a	16/25	64.0	16/16	100	16/16	100	16/16	100
	F1b	16/21	76.2	16/16	100	16/16	100	15/16	93.8
	F2a	13/53	24.5	13/16	81.2	13/13	100	13/13	100
	F2b	13/25	52.0	12/13	92.3	12/13	92.3	12/12	100
	F3a	17/69	24.6	11/16	68.8	11/17	64.7	10/11	90.9
	F3b	12/29	41.4	10/11	90.9	10/12	83.3	10/10	100
10	F1a	17/42	40.5	16/16	100	16/17	94.1	16/16	100
	F1b	16/23	69.6	16/16	100	16/16	100	16/16	100
	F2a	12/54	22.2	12/16	75.0	12/12	100	12/12	100
	F2b	10/28	35.7	10/12	83.3	10/10	100	10/10	100
	F3a	13/63	20.6	12/16	75.0	12/13	92.3	12/12	100
	F3b	12/34	35.3	11/12	91.7	11/12	91.7	11/11	100
100	F1a	14/53	26.4	14/16	87.5	14/14	100	13/14	92.9
	F1b	14/31	45.2	14/14	100	14/14	100	14/14	100
	F2a	16/54	29.6	13/16	81.2	13/16	81.2	13/13	100
	F2b	12/32	37.5	12/13	92.3	12/12	100	11/12	91.7
	F3a	16/52	30.8	13/15	86.7	13/16	81.2	12/13	92.3
	F3b	12/40	30.0	10/10	100	10/12	83.3	10/10	100

Note: Mating Index = $\frac{\text{Number of Copulations}^a}{\text{Number of Estrus Cycles Req'd.}} \times 100$ Fertility Index = $\frac{\text{No. of Pregnancies}}{\text{No. Of Copulations}} \times 100$

Incidence of Pregnancy = $\frac{\text{No. of Pregnancies}}{\text{No. of Females Mated}} \times 100$ Incidence of Parturition = $\frac{\text{No. of Parturitions}}{\text{No. of Pregnancies}} \times 100$

[a] Only one copulation was counted during one estrous cycle of 5 days.

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TABLE 2

Survival Indices of Progeny of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Dietary Level (ppm)	Litter	Live Birth Index	24 - Hour Survival Index	5 - Day Survival Index	Lactation Index
None - Control	F1a	92.7	88.5	42.4	93.9
	F1b	93.4	98.9	65.7	64.1
	F2a	95.2	94.3	64.3	81.2
	F2b	100	99.3	82.3	73.9
	F3a	90.2	97.8	75.0	78.5
	F3b	85.3	97.8	85.0	56.0
Aroclor 1242	F1a	94.6	98.3	59.2	97.8
	F1b	92.8	97.2	82.2	71.7
1	F2a	97.5	98.7	69.5	76.8
	F2b	95.5	95.0	71.4	74.4
	F3a	87.2	92.0	61.3	64.1
	F3b	88.8	93.0	63.4	51.1
	F1a	98.3	98.3	76.9	91.5
	F1b	98.1	99.5	80.3	79.1
10	F2a	93.7	92.4	81.4	85.6
	F2b	96.3	99.2	86.4	71.8
	F3a	85.2	99.2	82.7	99.0
	F3b	94.1	95.0	74.4	85.3
	F1a	92.9	95.5	85.3	77.9
100	F1b	98.5	98.0	66.5	53.2
	F2a	84.9	82.2	80.0	97.2
	F2b	80.8	93.8	93.8	84.6

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TABLE 2 (Continued)

Survival Indices of Progeny of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Dietary Level (ppm)	Litter	Live Birth Index	24 - Hour Survival Index	5 - Day Survival Index	Lactation Index
Aroclor 1254	F1a	99.5	97.8	88.7	93.1
	F1b	97.6	78.7	91.6	78.8
1	F2a	100	99.2	90.2	83.0
	F2b	97.6	99.1	85.1	88.1
	F3a	82.4	84.3	81.4	88.7
	F3b	92.5	100	95.5	90.5
	F1a	90.8	96.6	77.0	83.7
	F1b	90.1	91.9	86.7	85.5
10	F2a	94.8	71.7	58.7	84.0
	F2b	98.9	75.8	50.0	94.6
	F3a	93.9	98.9	95.7	80.5
	F3b	89.0	94.3	88.6	84.2
	F1a	100	94.6	58.7	69.6
	F1b	93.3	97.4	72.4	25.7
100	F2a	88.7	88.2	64.7	62.7
	F2b	84.5	74.4	53.7	62.5
	F3a	81.1	70.1	18.2	64.3
	F3b	95.2	97.5	49.4	51.3

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TABLE 2 (Continued)

Survival Indicies of Progeny of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Dietary Level (ppm)	Litter	Live Birth Index	24 - Hour Survival Index	5 - Day Survival Index	Lactation Index
Aroclor 1260	F1a	97.1	97.5	76.8	93.0
	F1b	91.9	100	82.9	60.2
1	F2a	99.2	98.4	83.6	93.2
	F2b	100	100	77.9	83.5
	F3a	90.8	96.2	74.7	74.1
	F3b	98.9	98.9	70.8	93.0
	F1a	99.5	98.4	96.2	95.9
	F1b	98.1	99.5	97.1	87.7
10	F2a	99.2	91.7	86.0	80.6
	F2b	99.1	96.5	67.0	85.7
	F3a	93.1	81.9	71.3	88.0
	F3b	93.5	95.3	51.2	78.6
	F1a	98.8	91.2	67.8	90.2
	F1b	85.6	94.2	69.3	75.6
100	F2a	97.8	90.1	81.1	76.8
	F2b	99.2	88.9	88.1	83.8
	F3a	86.4	98.9	90.5	84.3
	F3b	89.8	97.7	75.0	50.8

Note: Live Birth Index = $\frac{\text{No. of Viable Pups Born}}{\text{Total No. of Pups Born}} \times 100$

24-Hour Survival Index = $\frac{\text{No. of Pups Viable at Day 1}}{\text{No. of Viable Pups Born}} \times 100$

5-Day Survival Index = $\frac{\text{No. of Pups Viable at Day 5}}{\text{No. of Viable Pups Born}} \times 100$

Lactation Index = $\frac{\text{No. of Viable Pups at Day 21}}{\text{No. of Pups Viable at Day 5}} \times 100$

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TABLE 3

Body Weight Data for Gravid Albino Rats Treated with

Aroclors 1242, 1254 and 1260

Test Material	Dosage Level (mg/kg)	Body Weight (grams) on Gestation Day 6	9	12	15	20	Total Weight Gain (grams)
None	—	208	228	255	273	312	104
Aroclor 1242	10	210	226	245	273	344	134
	30	190	203	211	244	309	119
Aroclor 1254	10	204	211	213	238	275	71
	30	204	209	228	242	292	88
Aroclor 1260	10	198	206	237	255	283	85
	30	195	200	231	247	280	85

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TABLE 4

Reproductive Effects of Aroclors 1242, 1254 and 1260

in Albino Rats

Test Material	Dose Level (mg/kg)	Females Examined	Corpora Lutea mean/female	Inplantation Sites mean/female	Resorption Sites mean/female	Viable Fetuses mean/female	Females with one or more resorptions percent
None	—	26	11.7	10.3	0.5	9.8	23.1
Aroclor 1242	10	22	12.2	11.1	0.7	10.4	54.5
	30	20	12.0	11.0	0.2	10.8	15.0
Aroclor 1254	10	18	10.7	9.5	0.7	8.8	61.1
	30	18	11.6	10.2	0.8[a]	9.4	44.4
Aroclor 1260	10	17	12.4	11.2	0.5	10.8	29.4
	30	19	11.7	10.7	1.2[b]	9.5	57.9

[a] One female had six resorption sites.
[b] One female had 12 resorption sites.

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TABLE 5

Skeletal Development of Progeny of Albino Rats Treated with

Aroclors 1242, 1254 and 1260

Test Material	Dose Level mg/kg	FINDINGS A I	A P	B I	B P	C I	C P	D I	D P	E I	E P	F I	F P
None	—	8	4.7	30	17.8	23	13.6	1	0.6	58	34.3	111	65.7
Aroclor 1242	10	1	0.8	5	3.8	5	3.8	—	—	11	8.4	120	91.6
	30	1	0.7	15	10.5	22	15.4	—	—	37	25.9	106	74.1
Aroclor 1254	10	2[a]	1.8	12	10.6	22	19.5	—	—	33	29.2	80	70.8
	30	1	1.0	21	20.4	17	16.5	—	—	37	35.9	66	64.1
Aroclor 1260	10	1	0.8	20	15.5	9	7.0	—	—	27	20.9	102	79.1
	30	1	0.9	21	18.6	15	13.3	—	—	31	27.4	82	72.6

A = Supernumerary ribs
B = Incomplete ossification of sternum section (s)
C = Non-ossified sternum section (s)
D = Underdeveloped frontal and parietal skull bones
E = Abnormal fetuses
F = Normal fetuses
I = Incidence
P = Percent
[a] Angulated ribs

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TABLE 6

Internal Development of Progeny of Albino Rats Treated with Aroclors 1242, 1254 and 1260

Test Material	Dose Level mg/kg	Findings	Incidence	Percent
None	—	Small atria	6	7.1
		Large atria	7	8.2
		Undescended testes	2	2.4
Aroclor 1242	10	Small atria	4	4.1
		Large atria	12	12.2
		One small testicle	2	2.0
	30	Small atria	2	2.7
		Large atria	11	15.1
		One small testicle	3	4.1
Aroclor 1254	10	Small atria	1	2.1
		Large atria	10	21.7
	30	Small atria	5	7.6
		Large atria	1	1.5
		Caudal renal ectopia	8	12.1
Aroclor 1260	10	Small atria	1	1.9
		Large atria	11	20.4
	30	Moderate internal hydrocephalus	1	1.5
		Small atria	11	16.4
		Large atria	5	7.5

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FOOTNOTES

[1] Aroclors 1242, 1254 and 1260. Monsanto Company, St. Louis, Missouri

[2] Present address: 624 N. Abrego Drive, Green Valley, Arizona 85614

[3] Monsanto Company, St. Louis, Missouri

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STLCOPCB4019501