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SUMMARY OF TOXICOLOGICAL STUDIES ON COMMERCIAL PCB's

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The urgent need for additional toxicological data became apparent when the refinement of analytical techniques made possible the identification of PCBs in many portions of the ecosystem.

To assess the biological hazards of these materials, chronic feeding studies in rats and dogs were conducted according to accepted traditional procedures with Aroclors 1242, 1254 and 1260. It should be pointed out that Aroclor 1260 is no longer produced in this country since it does not meet the physical specifications for its restricted uses (ref. 1).

In addition, three generation two litter reproduction and teratology studies in albino rats as well as a dominant lethal mutagenic study in albino mice were considered to be necessary for the broad spectrum safety evaluation of these materials.

Effects such as decreases in eggshell thickness described in certain avian species suggested that toxicity and reproduction studies in chickens would be helpful in evaluating possible untoward effects in birds.

A list of the studies conducted are presented in figure 1.

The experimental design of the chronic rat and dog studies is given in figures 2 and 3. It should be noted that these studies were of typical Food and Drug Administration design for the evaluation of the safety of direct and indirect food additives.

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The important results in the chronic rat studies which were conducted on Charles River rats are summarized briefly in figures 4, 5 and 6.

Food consumption, mortality and hematologic, urine and blood chemistry studies did not differ among treatment and control groups. The only weight depression observed was at the 24 month point in females fed 100 ppm of Aroclor 1254.

Liver weight increases were noted in males and females fed 100 ppm Aroclor 1254 or Aroclor 1260, and in females only in the 100 ppm group fed Aroclor 1242.

As expected, the important histopathologic changes in the rat study were present in the livers of the 24 month sacrifice animals and consisted of hepatocellular alterations such as focal hypertrophy, cytoplasmic lipid changes and in some animals at 100 ppm, hepatomas or cholangiohepatomas. No evidence of hepatocellular carcinogenicity of the Aroclors was found in this study.

The conclusion that "no evidence of hepatocellular carcinogenicity of the Aroclors was found in this study" was reached only after extensive re-evaluation of the original liver slides as well as additional liver sections from all of the animals after the Kimbrough results on Aroclor 1260 became known to us (ref. 2).

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The slides were read independently and separately by Dr. Donovan Gordon (ref. 3), Professor Ward Richter (ref. 4), and by Professor P. Pour (ref. 5) of Industrial BIO-TEST Laboratories, the University of Chicago, and the Eppley Institute for Cancer Research, respectively.

The interpretation of pathologic changes that occur in the liver as a result of absorption of chlorinated hydrocarbons is a key issue that needs resolution by the community of pathologists (refs. 6-7).

The problem is highlighted in the context of PCBs since there appears to be disagreement as to whether Aroclor 1260 is or is not a hepatocellular carcinogen (ref. 8). Pour re-evaluated the Kimbrough slides and does not agree with the reported findings.

The findings in the chronic dog study are summarized in figure 7. The feeding of Aroclor 1260 at 100 ppm showed an increase in serum alkaline phosphatase activity and liver weights. A slight decrease in body weight gain was noted at the 100 ppm dose level in males and at 10 and 100 ppm in females. No remarkable histopathologic changes were found. However, evidence of gastrointestinal inflammatory lesions and ulcerations was noted which appear to be similar to those found by Allen in the rhesus monkey by feeding Aroclor 1248 (ref. 9). (This material is no longer a product of commerce (ref. 1).)

The design of the dominant lethal mutagenic study is presented in figure 8.

No effects related to Aroclor treatment were seen in the parameters listed in figure 9 - mortality, mating index, number of implantation and resorption sites, number of viable embryos, pre-implantation loss or mutation rates. This finding is in agreement with that of Green et al. (ref. 10).

The standard design for a three generation two litter reproduction study in albino rats is given in figure 10 and the teratology study in figure 11.

A brief summary of the results (figure 12) indicates that none of the Aroclors studied produced adverse effects in the two litters of the first generation.

All progeny delivered by female rats in each of 3 generations exposed to dietary levels of up to 100 ppm of either Aroclor 1242, 1254 or 1260 were structurally normal. A reduction in the mating index was observed in the 2nd and 3rd generations of animals fed either 10 or 100 ppm. The ability of females to conceive, carry the delivery process to parturition, and to successfully nourish the young was not affected by the 3 Aroclors. It should be stressed that no changes in the reproductive tract of either male or female rats were produced by any of the 3 Aroclors. Findings in the 3rd generation were similar to those in the 1st with no suggestion of any alterations in response as a function of succeeding generations.

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Teratologic studies in which albino rats were exposed to either Aroclor 1242, 1254 or 1260 at doses of up to 30 mg/kg during rapid organogenesis - gestation days 6 through 15 - were conducted in our laboratories. No evidence of embryotoxicity as reflected by an increase of fetal resorption or teratogenicity as measured by complete external, skeletal, and internal evaluation of fetuses obtained from the Aroclor-treated females, was obtained. Other experimental data pertaining to the potential teratogenicity of polychlorinated biphenyls supports the lack of adverse effects. Mizunuya (ref. 11) and his colleagues found no evidence of teratogenicity in the rat when fed at dietary levels of up to 250 ppm. In the mouse, Toeruek (ref. 12) found that doses of up to 500 mg/kg was non-teratogenic although when given on gestation days 1 through 6, a decrease in implantation sites and fetal weights was observed. These doses given on gestation days 7 through 11 failed to produce any changes with respect to either reproductive parameters or teratogenicity. Further, no evidence of malformation was obtained in infant monkeys delivered to females fed either 2.5, 5 or 25 ppm Aroclor 1248 although the birth weights were reported to be reduced (ref. 9).

The last study in this series was a toxicity/reproduction study in white Leghorn chickens (figures 13, 14 and 15).

Aroclor 1260 at all test levels did not produce adverse effects on the various parameters investigated. Egg production in hens fed

100 ppm Aroclor 1242 or 1254 was decreased as was egg hatchability. In fact, poor hatchability of eggs from hens fed 8 ppm Aroclor 1242 was found (figure 15).

In addition, Aroclor 1242 at 10 and 100 ppm and Aroclor 1254 at 100 ppm were associated with reduced eggshell thickness. Chick viability was affected by both substances at the 10 ppm dose level.

Conclusions

1. The no-effect level for the Aroclors in the chronic rat and dog studies is about 10 ppm.
2. No teratogenic or mutagenic effects were found.
3. No hepatocellular carcinomas were present.
4. The no-effect level in the rat reproduction study is between 1 and 10 ppm and is the result of low mating indices.
5. In the chicken reproduction and teratology studies, effects were more severe with Aroclor 1242 with the no-effect level being 2 - 4 ppm.

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Figure 1

TOXICITY STUDIES CONDUCTED WITH AROCLORS 1242, 1254 AND 1260

Two-Year Chronic Oral	Albino Rats
Two-Year Chronic Oral	Beagle Dogs
Three-Generation Reproduction	Albino Rats
Teratology	Albino Rats
Dominant Lethal Mutagenic	Albino Mice
Toxicity / Reproduction	White Leghorn Chickens

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Figure 2

TWO-YEAR CHRONIC ORAL TOXICITY STUDY
ALBINO RATS AND BEAGLE DOGS

Test Material	Dietary Levels (ppm)	Number of Animals per Dietary Level			
		Rats		Dogs	
		M	F	M	F
None	– – –	50	50	4	4
Aroclor 1242	1, 10, 100	50	50	4	4
Aroclor 1254	1, 10, 100	50	50	4	4
Aroclor 1260	1, 10, 100	50	50	4	4

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Figure 3

TWO-YEAR CHRONIC ORAL TOXICITY STUDY
ALBINO RATS AND BEAGLE DOGS

Parameters Investigated:

- Body Weight
- Food Consumption
- Hematology
- Clinical Blood Chemistry (BUN, SAP, SGPT, fasting blood glucose, SGOT — dogs only)
- Urinalyses
- Pathology (gross, organ weights, microscopic)

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Figure 4

INGESTION OF AROCLOR 1242—ALBINO RATS
LIVER EFFECTS

Increase in Liver Weights — 100 ppm — Females

Primary Liver Lesions

None at 3, 6, 12 month sacrifice

24 month sacrifice—100 ppm—Increased incidence of:

Nodular Hyperplasia	(8 / 20)
Hepatoma	(2 / 20)
Cholangiohepatoma	(1 / 20)
Hepatocellular Carcinoma	(0 / 20)

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Figure 5

INGESTION OF AROCLOR 1254—ALBINO RATS
LIVER EFFECTS

Increase in Liver Weights — 100 ppm

Primary Liver Lesions

None at 3, 6, 12 month sacrifice

24 month sacrifice — 100 ppm — Increased incidence of:

Nodular Hyperplasia	(13/27)
Hepatoma	(4/27)
Cholangiohepatoma	(2/27)
Hepatocellular Carcinoma	(0/27)

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Figure 6

INGESTION OF AROCLOR 1260 – ALBINO RATS
LIVER EFFECTS

Increase in Liver Weights — 100 ppm

Primary Liver Lesions

None at 3, 6, 12 month sacrifice

24 month sacrifice – 100 ppm – Increased incidence of:

Nodular Hyperplasia	(7 / 27)
Hepatoma	(5 / 27)
Cholangiohepatoma	(2 / 27)
Hepatocellular Carcinoma	(0 / 27)

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Figure 7

EFFECTS OF INGESTION OF AROCLORS — BEAGLE DOGS

Aroclor 1242 —— no effects

Aroclor 1254 —— slight decrease in body weight gain
- 100 ppm

Aroclor 1260 —— slight decrease in body weight gain
- 100 ppm males
- 10 and 100 ppm females

—— increase in SAP - 100 ppm

—— increase in liver weights - 100 ppm

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Figure 8

DOMINANT LETHAL MUTAGENIC STUDY — ALBINO MICE

Test Material	Dose*
Corn Oil	0.9 ml / kg
Methyl methane sulfonate (MMS)	100 mg / kg
Aroclor 1242	500 or 1000 mg / kg
Aroclor 1254	500 or 1000 mg / kg
Aroclor 1260	500 or 1000 mg / kg

*single dose given i.p. to 12 males / group

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Figure 9

DOMINANT LETHAL MUTAGENIC STUDY — ALBINO MICE

No effects related to Aroclor treatment seen in:

- Mortality
- Mating index
- Number of implantation sites
- Number of resorption sites
- Number of viable embryos
- Pre-implantation loss
- Mutation rates

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Figure 10

THREE-GENERATION REPRODUCTION STUDY*—ALBINO RATS

Test Material	Dietary Levels (ppm)	Number of Animals per Dietary Level	
		M	F
None	— — —	8	16
Aroclor 1242	1, 10, 100	8	16
Aroclor 1254	1, 10, 100	8	16
Aroclor 1260	1, 10, 100	8	16

*Two litters per generation

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Figure 11

TERATOLOGY STUDY — ALBINO RATS

Test Material	Dose* (mg/kg/day)	Number of Gravid Rats
Corn Oil	—	26
Aroclor 1242	10 or 30	26
Aroclor 1254	10 or 30	26
Aroclor 1260	10 or 30	26

*administered on gestation days 6 through 15 (10 doses)

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Figure 12

EFFECT OF AROCLORS ON REPRODUCTION / TERATOLOGY -ALBINO RATS

1. Reproduction Study

   First generation — no effects

   Second and Third generations — 10 and 100 ppm

   — decrease in mating index

   — decrease in incidence of pregnancy

   (Aroclor 1242 - no third generation with 100 ppm)

2. Teratology Study — no effects

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Figure 13

TOXICITY / REPRODUCTION STUDY — WHITE LEGHORN CHICKENS

Test Material	Dietary Levels (ppm)	Number of Animals per Dietary Level	
		M	F
None	—	8	40
Aroclor 1242	1, 2, 4, 8, 10, 100	4	20
Aroclor 1254	1, 10, 100	4	20
Aroclor 1260	1, 10, 100	4	20

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Figure 14

TOXICITY / REPRODUCTION STUDY — WHITE LEGHORN CHICKENS

Parameters investigated :

body weight
food consumption
egg production
egg quality
egg hatchability
eggshell thickness
chick body weight
chick viability
pathology

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Figure 15

EFFECTS OF AROCLORS ON CHICKEN REPRODUCTION

Parameter	Dietary Level Causing Effect	
	1242	1254
Egg Production	100	100
Egg Hatchability	8	100
Shell Thickness	100	100
Chick Viability	10	10

Aroclor 1260 — no effects at any dose level

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