Toxicity and Environmental Effects of Commercial PCBs

Introduction

Polychlorinated biphenyls (PCBs) are not a single chemical entity. They are produced by chlorinating biphenyl to acheive a final product with specified properties. These products, sold under the trade name AROCLOR by Monsanto, are mixtures of chlorine-containing biphenyls with different numbers and positions of the chlorine substituents.

Over the years, a series of investigations have been conducted to assess potential health and environmental hazards of PCBs. The 3 predominant commercial mixtures (AROCLORS 1242, 1254 and 1260) have been studied most intensively. Toxicity tests performed on these 3 commercial mixtures were typical in scope of those designed for the evaluation and establishment of the safety of direct and indirect food additives.

It may be noted that AROCLOR 1260 no longer is produced in this country since it does not meet the physical specifications for its restricted uses.

Conclusions Based on Monsanto Studies

1) As a class, the AROCLORS are relatively harmless materials for routine industrial handling under ambient conditions.

2) Threshold Limit Values of 1 mg/m^3 and 0.5 mg/m^3 have been established for materials containing average chlorine values of 42% and 54%, respectively, of the available sites.

3) The no-effect level for these materials in chronic

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rat and dog feeding studies is about 10 ppm in the diet. No hepatocellular carcinomas were present.

4) The no-effect level on rat reproduction is between 1 and 10 ppm in the diet since higher levels result in low mating indices.

5) No teratogenic or mutagenic effects were observed in studies with rats and mice.

6) In chicken reproduction and teratology studies, AROCLOR 1242, which produced the most severe effects, had a no-effect level of 2-4 ppm in the diet.

7) Acute toxicity to fish varies from less than 1 ppm to greater than 100 ppm depending on the specific AROCLOR and species of fish tested.

8) PCBs containing 3 or less chlorine substituents per molecule are reasonably biodegradable.

Summary of Monsanto's Long-term Toxicity Studies on Commercial PCBs.

These tests consisted of 2-year (lifetime) feeding to rats, 2-year feeding to dogs, 3-generation rat reproduction studies with 2 litters cast per generation, rat teratology studies and dominant lethal mutagenic studies in mice. Toxicity and reproduction studies in chickens were performed to evaluate possible untoward effects in birds such as decreases in eggshell thickness. In addition, biodegradation and tissue accumulation studies have been conducted.

The highest dietary level (100 ppm) in the lifetime rat feeding studies produced a weight depression at 24 months in females fed AROCLOR 1254 and liver weight increases in all

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groups except males fed AROCLOR 1242. As with other halogenated hydrocarbons, the important histopathologic changes were present in the livers of animals sacrificed at the end of the study. These consisted of hepatocellular alterations such as focal hypertrophy, cytoplasmic lipid changes and in some animals from the 100 ppm groups, hepatomas or cholangiohepatomas. No evidence of hepatocellular carcinogenicity of the AROCLORS was found.

In the dog 2-year studies, some slight decreases in body weight gain were noted. At the highest feeding level (100 ppm), AROCLOR 1260 produced an increase in serum alkaline phosphatase activity and liver weights without concomitant histopathologic changes. However, there was evidence of gastrointestinal inflammatory lesions and ulcerations which appear to be similar to those found by Allen in rhesus monkeys fed AROCLOR 1248. (AROCLOR 1248 was an experimental product which never was commercialized.)

In the rat reproduction studies, none of the AROCLORS produced adverse effects in the 2 litters of the first generation. In the second and third generations, there was a reduction in the mating index at the 2 highest feeding levels (10 ppm and 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. No changes were produced in the reproductive tracts of either male or female rats by any of the 3 AROCLORS.

There was no evidence of teratogenic or mutagenic changes with any of the PCBs at maximally tolerated dose levels in

rats and mice.

In the chicken toxicity/reproduction study, AROCLOR 1260 was without effect at all test levels. AROCLORS 1242 and 1254 at 100 ppm in the diet decreased egg hatchability. In fact, poor hatchability of eggs was found from hens fed 8 ppm of AROCLOR 1242. 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 a dietary level of 10 ppm.

Biodegradation studies were conducted using semi-continuous activated sludge systems and tissues of rats fed PCBs were analyzed to measure accumulation and retention of these materials. These factors are influenced by the number and position of the chlorine substituents. Higher chlorine-containing members are more resistant to biodegradation and they accumulate more readily and are less readily metabolized and/or excreted from lipoid tissue in animals. PCBs containing 3 or less chlorine substituents per molecule are reasonably biodegradable.

Comments

The conclusion that "No evidence of hepatocellular carcinogenicity of the AROCLORS was found" in the 2-year rat feeding 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. The slides were read

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independently by Dr. D. Gordon of Industrial BIO-TEST Laboratories, Professor W. Richter of the University of Chicago, and by Professor P. Pour of the Eppley Institute for Research in Cancer. In addition, Dr. Pour evaluated the Kimbrough slides and does not agree with the reported findings.

Barsotti and Allen have reported that 2.5 ppm of AROCLOR 1248 in the diet of rhesus monkeys adversely affected reproduction. This approximates a dosage of 100 μg/kg/day. It is higher than the safe human intake (1 μg/kg/day) estimated by FDA from human data when it promulgated its tolerances for PCBs in food.

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Human data

(F.R. July 6, 1973. p. 18097, Section (2))

Lowest level of PCBs producing effect in man = 500 mg total.
500 mg consumed by 50 kg individual over 50 days.
500 mg ÷ 50 kg ÷ 50 days = 200 µg/kg/day (effect level)
Using 10-fold safety factor leads to estimate that 20 µg/kg/day may be safe over a 50-day interval.
Since PCBs have long half-life; calculating same intake over a 22-month span arrives at an estimated safe intake for a protracted period of 1 µg/kg/day.

Primate data

(Fed. Proc. 34:338 (1975). Abstract 675. Barsotti & Allen)

At 2.5 ppm in diet, primates ingested 182 mg over 52 weeks.
182 mg ÷ 365 days = 0.5 mg/day which produced effects.
Assuming 5 kg primate, 500 µg ÷ 5 kg = 100 µg/kg/day
Conclusions: Primate study done at dosages (100 µg/kg/day) greater than the safe dosage (1 µg/kg/day) esimated from human data.
Primate study does show effects at lower dosages over longer time span (100 µg/kg/365 days) than had been observed in man (200 µg/kg/50 days).
The total amount of PCBs producing effects in primates (182 mg) was lower than that producing effects in man (500 mg).

(N.B. Abrahamson & Allen, Env. Health Perspectives. June, 1973, 81-86. Report that infant monkeys are able to tolerate doses of PCBs that produce extreme morbidity in adult monkeys.)

Dog and Rodent Data

(F.R. July 6, 1973. p. 18097, Section (1))

"No-effect" level for man using a 100-fold safety factor and accepting 10 ppm as a "no-effect" level in animals would be 2.5 µg/kg/day based on dog data and 3 µg/kg/day based on rat data.
If rat data "no-effect" level drops to 1 ppm, then corresponding estimate of human "no-effect" level drops to 0.3 µg/kg/day.
Question: In a "collision" between rat data using a 100-fold safety factor and human data using a 10-fold safety factor, which data base would you like to be riding on?
Comment: Since human data is available, it could be argued that the traditional 100-fold safety factor is not necessary. Application of a 30-fold safety factor to rat data, supported by dog and human data, makes present estimate of safe human intake appear reasonable.

PCB Primate and Human Residue Data

	Primates		Human
Conc. in diet, ppm	25	2.5	-
Intake, µg/kg/day	800	100	-
Estimated safe dose, µg/kg/day		-	-/
Liver conc., µg/g	56.3(0.01)*		-
Fat conc., µg/g	50.0(27.7)*		0 (314 samples)**
			<1 (125 samples)
			1-2 (165 samples)
			>2 (33 samples)

*Value in ( ) from infant primate.
Allen et al., TAP 30: 440-451 (1974)

**Yobs, Env. Health Persp.,79-81, April 1972

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