

Appendix B
Section N

POLYCHLORINATED BIPHENYLS
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

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EXECUTIVE SUMMARY

Polychlorinated biphenyls (PCBs) have been used commercially for over fifty years primarily as dielectrics. Their chemical inertness and lipophilicity have led to their wide dissemination and persistence in the environment. Human exposure to PCBs has resulted largely from consumption of contaminated food and from the work environment. PCBs accumulate in the fatty tissues and skin of man and other animals. The major sites of pathology caused by PCBs are the skin and liver. The degree of chlorination and the amount of contamination of PCB mixtures with polychlorinated dibenzofurans contribute significantly to the degree of toxicity. Several studies in rodents suggest strongly that PCBs are carcinogenic and may also enhance the carcinogenicity of other compounds. The multistage model was used to estimate a level of risk for the human population from cancer. A maximum level of PCBs in drinking water of 0.024 ug/L was projected to result in no more than 1 excess cancer in 10^6 individuals (upper bound estimate) exposed to that level for a lifetime.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

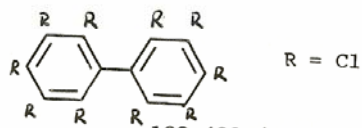
Chemical name: Polychlorinated Biphenyls (PCBs)

CAS#

1336-36-3

PCBs consist of compounds with a biphenyl backbone substituted by varying amounts of chlorine atoms on the aromatic rings. As many as 209 different compounds (congeners) of PCBs are possible; they exist in varying proportions in commercial mixtures called Aroclor (U.S.), Kanechlor (Japan) and Clophen (Germany). Commercial PCB mixtures are distinguished by a number, eg. Aroclor 1254, which is based on the average percentage of chlorine in the mixture.

Chemical Structure



Molecular weight range:

188-490 (Aroclor 1254: 324)

Physical state: Lower-chlorinated PCBs are colorless mobile oils. Higher-chlorinated PCBs vary from viscous liquids to sticky resins.

Melting point: with the exception of Aroclors 1268, 1270, which are off-white powders, Aroclors do not crystallize.

Boiling Point (Aroclor 1254):

340-375 °C

Vapor pressure (Aroclor 1254):

4.94×10^{-4} mm/Hg

Specific gravity, density:

high

Water Solubility (Aroclor 1254):

50 ug/L at 25 °C

Octanol and water partition coefficient:

10,000-20,000 for lower chlorinated PCBs.

Odor threshold, water:

odorless

Production and Use

Production of PCBs is banned; however there are a few exceptions. The sole U.S. producer of PCBs marketed several Aroclors for use in closed electrical systems. Prior to 1971, PCBs also were used in plasticizers, heat transfer fluids, hydraulic fluids, fluids in vacuum pumps and compressors, lubricants and wax extenders. It is expected that due to the

long life of PCBs, a substantial portion of those which were made before the current ban, are still in service and may continue to pose an environmental risk (U.S.EPA, 1980).

Guidelines, Regulations, and Standards

Based on acute and chronic PCB toxicity studies on aquatic life, the U.S. Environmental Protection Agency (U.S.EPA) has developed, according to its "Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life", the following criteria:

Freshwater: 0.0014 ug/L on a 24 hr. average.

Saltwater: 0.030 ug/L on a 24 hr. average (U.S.EPA, 1980).

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a TWA and STEL for Aroclor 1254, respectively, and 1 and 2 mg/m³ for Aroclor 1242 (ACGIH, 1980).

The National Institute for Occupational Safety and Health (NIOSH) criterion for PCBs in the workroom air is 1.0 ug/m³ for 10 hours per day, 40 hours per week exposure (NIOSH, 1977).

The Toxic Substances Control Act (TSCA) restricted the manufacture, sales, and distribution of PCBs on October 11, 1977. Manufacture was banned January 1, 1979 and distribution by July 4, 1979. Allowances for certain exceptions were provided. The Food and Drug Administration (FDA) established tolerance levels in foods at 1.5 ppm in milk, 3.0 ppm in poultry and 2 ppm in fish (U.S.EPA, 1980).

The water quality criterion for protection of human health due to exposure to PCB's is 0.079 ng/L, based on estimates of the 10⁻⁶ excess carcinogenic risk (upper bound) associated with lifetime exposure to PCBs in drinking water and from consumption of fish (U.S.EPA, 1980).

ENVIRONMENTAL EXPOSURE

Fate and Transport

The environmental fate of various PCB mixtures is strongly related to their chemical properties. The lower-chlorinated mixtures are more volatile and soluble than the higher-chlorinated ones, thereby they are more mobile in the environment. However, the higher chlorinated PCBs are also widely dispersed but for different reasons. They adsorb strongly to sediments and particulates in the environment, and because of their lipophilicity they concentrate in the fatty tissues of organisms. This bioconcentration, as well as the difficulty in metabolizing the higher chlorinated PCBs by these organisms, leads to accumulation of PCBs through the food chain.

PCBs are very resistant to most chemical reactions except under the most extreme conditions. Under environmental conditions, PCBs, especially the lower chlorinated ones, appear to undergo alkali- and photochemically-catalyzed nucleophilic substitutions as well as photochemical free radical substitutions; all of them occur with alkali and water. Hydroxylation of the phenyl rings appears to be promoted by metals and their salts. These processes may account for the occurrence of polychlorinated dibenzofurans (PCDFs) which commonly contaminate PCB mixtures.

Ambient Levels

It has been estimated that between 1930-1970 PCB emission levels were: 3×10^4 tons to air, 6×10^4 tons to fresh and coastal waters, 3×10^5 tons to dumps and landfills. One-third of the PCBs in air and one-half of the PCBs in water have probably been degraded (U.S.EPA, 1980).

Routes of exposure to the general population are principally through water and food. Dermal contact and air are principle routes of industrial exposure. The low solubilities of PCBs, especially the PCB isomers with a higher degree of chlorination, prevent them from reaching high levels in drinking water.

The FDA and the Department of Agriculture (USDA) have monitored PCBs in food since 1969 and have reported that the highest and most consistent levels appear in finfish. Maximum levels of up to 35 ppm for finfish and 22.8 ppm for milk have been recorded (Jelinek and Corneliussen, 1976). Ingestion of freshwater fish is the most significant source of exposure for the general population.

Median water levels of PCBs range from 0.1 to 0.3 ug/L in positive samples; the frequency of detection is 0-20% of all samples in the U.S. (Dennis, 1976). Average intake of PCBs in the U.S. was estimated to be 9 ug/day in the mid 1970s, with fish being the major dietary source (Kutz and Yang, 1976)

PCBs may be found in the atmosphere either in the gaseous state or adsorbed to airborne particles. Distribution of PCBs in air is nonuniform and is concentrated mostly in urban areas. Average atmospheric levels in Florida and Colorado were 100 ng/m^3 (Kutz and Yang, 1976). Average fallout along the Southern California coast was estimated to be 1800 kg per year over a $50,000 \text{ km}^2$ area.

The Office of Science and Research sampled public water supplies statewide for toxic substances from 1978 to 1981. Water contaminant levels for various PCB mixtures are reported in Table I (N.J.DEF, 1985).

Table I

PCB Levels in N.J. Public Water Supplies (N.J. DEP, 1985)

<u>Compound</u>	<u>Freq of Detection (%)</u>	<u>Detection Value (ug/L)</u>
Aroclor 1016	0.3	0.06
Aroclor 1232	0.2	0.06
Aroclor 1242	0.4	0.06
Aroclor 1248	0.6	0.20
Aroclor 1254	0.8	0.03

METABOLISM AND PHARMACOKINETICS

Absorption

Absorption of PCBs through the gut of rats and monkeys has been shown to be between 92-98% complete (Albro and Fishbein, 1972). Adult monkeys absorbed 90% of a single dose of 1.5 or 3 g/kg Aroclor 1248 from the gastrointestinal tract (Allen et al., 1974). Absorption via the respiratory tract and skin was also efficient (U.S.EPA, 1980).

Distribution

Upon ingestion, PCBs are first distributed and stored in liver and spleen and later are redistributed to skin and adipose tissue (Matthew and Anderson, 1975). PCBs have also been shown to be transferred transplacentally and sequestered in breast milk.

Metabolism and Excretion

Sequestering of PCBs in adipose tissue isolates them from metabolism, liver enzymes and greatly retards their clearance from the body.

Metabolism occurs through arene oxide intermediates, the formation of which is highly dependent upon the position of the chlorine atoms. PCBs are known to be potent inducers of mixed function oxidases. Final metabolic products of PCBs are phenolic or dihydrodiol derivatives which are conjugated and excreted through bile or urine. Approximately 90% of the metabolites are excreted (U.S.EPA, 1980).

Human Exposure and Body Burden

Yobs (1972) detected PCBs in 31.1% of the adipose tissue from 637 humans. The National Human Monitoring Program for Pesticides found PCBs in 1 to 40.3% of all adipose tissue tested (U.S.EPA, 1980). PCBs have also been found in 8 of 40 samples of breast milk from Colorado at levels of 40

to 100 ppb (U.S.EPA, 1980). PCB plasma levels were found in 43% of 723 samples taken in the mean of 2 to 3 ppb from the U.S. population (Finklea et al. 1972).

The population groups at particular risk to PCB exposure are those who are occupationally exposed, high consumers of fish, i.e. sport fisherman, and nursing infants. With the cessation of PCB manufacture, occupational exposure still exists for workers on PCB-containing transformers, capacitors, etc. Exposure due to accidental release remains a hazard since many PCB-containing units are still operational.

HEALTH EFFECTS

Overview

Most of the current knowledge regarding the toxicity of PCBs to humans stems from two significant outbreaks of human PCB exposure: in Japan, 1968 and Taiwan, 1979. In these instances, toxicity was characterized by hyperpigmentation, acneform eruptions, liver pathology, and gastrointestinal and neural effects. Infants from exposed mothers often show the same toxicity characteristics as adults, and additionally, retardation of growth and malformation of the skull, perhaps due to abnormal calcium deposition. Epidemiologic studies of workers exposed to PCBs have shown dermatitis and mild liver function abnormalities in the absence of any clinical illness. Several studies in rodents suggest that some PCBs are carcinogenic, and can enhance the carcinogenicity of other compounds. Polychlorinated dibenzofuran (PCDF) contaminants are breakdown products of PCBs and are thought to contribute significantly to the toxic effects seen with PCBs in both humans and animals.

Human

A well studied example of acute human exposure to PCBs is the 1968 Yusho (rice oil disease) episode in Japan. Rice oil was contaminated with 2 to 3 mg/kg of Kanechlor 400 (Kuratsune, 1972) through accidental leakage of the PCBs during processing. The average-ingested amount was 2 mg. High amounts of PCDFs in the oil were also found.

Yusho illness is initially characterized by increased eye discharge and acneform eruptions. Later symptoms included further dermatologic problems, swelling, jaundice, numbness of limbs, spasms, hearing and eye problems, as well as gastrointestinal disturbances. Laboratory evaluations showed a decrease in erythrocyte and an increase in leukocyte counts, as well as an increase in serum lipids. Liver biopsies showed hypertrophy of the endoplasmic reticulum and mitochondrial abnormalities. Decreased nerve conduction was seen in over a third of the patients. After three years, 50% of the patients were improving, 40% were unchanged, and 10% became more severely affected. Long term effects continued to be observed in children born to Yusho mothers. Dark brown skin and high plasma PCB levels were reported (Kuratsune et al., 1972).

The direct association of PCBs with the symptoms of Yusho/Yu Cheng patients came under question when high plasma levels of PCBs were discovered in a group of Japanese workers (Takamastu, et al., 1985). These workers had higher plasma concentrations of PCBs than typical Yusho patients, however they failed to exhibit most of the symptoms of Yusho disease. Clinical evaluations of these workers showed a few instances of chloracne and high levels of plasma triglycerides (Takamatsu et al., 1985). The PCB-contaminated oil which produced Yusho disease was known to contain high level of PCDFs (Nagayama et al., 1975); the same was observed with Yu Cheng (Chan et al., 1985). Tissues and blood from Yusho/Yu Cheng patients also were found to have high levels of PCDFs (Masuda et al., 1985). Therefore the studies conclude that PCDFs, and not PCBs, account for most of the symptoms of Yusho/Yu Cheng.

There have been several epidemiologic studies involving PCBs since 1978. Fischbein et al. (1979) reported that 50% of 326 capacitor manufacturing workers reported a history of dermatological symptoms. They also found no liver function abnormalities associated with exposure. The biochemical studies showed few abnormalities, none of them related to PCB levels.

In an exposed group of 120 railroad maintenance workers investigators found some cases of chloracne, but there was no significant association with blood levels. They reported liver functional abnormalities which were dose-related to blood PCB levels. There was also an association with triglyceride and blood PCB levels (Chase et al, 1982), .

Smith et al. (1982), in a study of 92 employees of two utility companies, formed no consistent association between dermatitis and high- or lower-chlorinated PCB levels. They also noted an association between the lower-chlorinated PCBs in the blood with liver-functional abnormalities in one of the plants, but not the other. Triglycerides were positively associated with high-chlorinated PCBs in one plant and negatively associated in the other, where they were positively associated with lower-chlorinated PCBs.

Animal

Acute. In rats, Bruckner et al. (1973) observed a 14 day LD₅₀ value of 4.25 g/kg. Toxic effects of high doses of Aroclor 1242 in rats included diarrhea, chromoacryorrhea, loss of body weight, unusual stance and gait, lack of response to pain stimuli, and terminal ataxia. Histopathologic changes were observed in the liver and kidney. More significant toxic effects were seen with repeated exposure over a period of time. Mink and adult Rhesus monkeys appear to be particularly sensitive to PCBs, with 30 ppm for 6 months producing 100% mortality in mink (U.S.EPA, 1980).

Chronic. The most consistent pathologic effect in mammals of chronically administered PCBs was fatty degeneration of the liver. Porphyria was observed in livers and in other organs but to a lesser

degree. PCBs were also recognized to induce strongly liver microsomal enzymes in rabbits, rats, and primates (U.S.EPA, 1980). Purified isomers have been shown specifically to induce either cytochrome P450 or P448 (Goldstein et al., 1978).

Other systemic effects include increased thyroxin metabolism, inhibition of ATPases and alteration of steroid hormone metabolism (U.S.EPA, 1980). PCBs have also been shown to have immunosuppressive effects in a number of species, however monkeys appear to be the most sensitive species (Allen et al., 1980).

A series of studies were conducted on female rhesus monkeys exposed to 0, 2.5, or 5 mg of Aroclor 1248/kg diet for 18 months and then extended an additional 21 months (Allen et al., 1980). At all levels of exposure females showed palpebral edema, erythema, alopecia, and acne. Females exposed to 2.5 mg/kg suffered extensive weight loss and irregular menstrual cycle length with depressed serum progesterone and estradiol levels. Monkeys exposed for 16 months to 2.5 mg/kg Aroclor 1258 showed altered serum chemistries, reduced total lipids, elevated serum glutamate pyruvate transferase (SGPT) and a shift in the ratio of albumin to globulin (A/G) (Barsotti, 1981).

Behavioral and Central Nervous System

Yusho victims complained about numbness of limbs, spasms, headaches, fatigue, as well as eye and ear problems. A decrease in sensory nerve conduction was seen in over a third of the patients hospitalized. There are reports that workers exposed to PCBs displaced systemic malaise and altered peripheral sensation, both of which correlated positively with blood PCB levels (Smith et al., 1982). Rats dosed with PCBs showed an unusual stance and gait indicative of central nervous effects (Bruckner, 1973).

Infant Rhesus monkeys exposed to PCBs (Aroclor 1248) in utero and in breast milk were given 11 behavioral tests; a positive correlation between reduced performance and increased PCB body burden was observed for seven tests (Bowman et al., 1978).

Reproductive, Embryotoxic, and Teratogenic

PCBs can readily cross the placental barrier and accumulate in fetal tissues. Children born to Yusho affected parents often showed the same toxic symptoms as their parents. Japanese investigators recently termed this condition fetal PCB syndrome, more commonly called "Coca Cola or Cola baby". This syndrome is characterized by dark brown pigmentation of skin and mucous membranes, gingival hyperplasia, exophthalmic edematous eye, dentition at birth, abnormal calcification of the skull, rocker bottom heel and low birth weight. Yusho affected infants also had a higher rate of mortality than normal children (Yamashita and Hayashi, 1985).

Women who consumed fish with high PCB levels were found to have high

PCB levels in maternal serum, milk, and cord blood. Infants born to these mothers had generally smaller birth weight and smaller head circumference than the controls born to mothers who did not eat fish (Fein et al., 1984).

In animals reproductive effects include decreased birth weight, decreased number of offspring and some indications of terata at maternal toxic doses. Female rhesus monkeys exposed to 0.01 or 0.02 mg/kg per day Aroclor 1248 for 7 months delivered young having reduced birth weight and focal areas of hyperpigmentation (Allen et al., 1979).

Genetic

A single PCB isomer, 4-chlorobiphenyl, was found to be mutagenic in *S. typhimurium* TA 1538 after liver microsomal activation (Wyndham et al., 1976). The amount of mutagenicity decreased with increasing degree of chlorination in this system. As discussed by Schoeny (1982), these results have not been replicated by other investigators. Schoeny (1982) found that PCBs are not mutagenic in bacterial test systems. Unscheduled DNA synthesis was induced by 4-chlorobiphenyl in Chinese hamster ovary cells which is an indication of DNA repair (U.S.EPA, 1980). A dominant lethal test with Aroclor 1242 and 1254 was performed in Osborne-Mendel rats (Green et al., 1975), but no significant treatment related effect was seen.

Although PCB isomers appear not to have genotoxic potential, PCB isomers and their metabolites do bind to macromolecules, including DNA, with varying degrees of affinity (U.S.EPA, 1980). This suggests that PCBs have the potential to cause alterations to the genome; however these alterations are not permanent. The ability of PCBs to induce enzymes responsible for metabolic activation of other known carcinogens may be the greatest genetic hazard posed by PCBs.

Carcinogenicity

Animal studies have shown a significant incidence of hepatic tumors and lesions with PCB treatment. As a result PCBs have been classified as B2 by the EPA (U.S.EPA, 1985) and 2B by the International Agency for Research on Cancer (IARC, 1982).

PCBs were first observed to produce cancers in old male mice given Kanechlor 500, 400, and 300 mixed in the diet at doses of 500, 250, and 150 ppm for 32 weeks. In 7 out of 17 male mice fed 500 ppm Kanechlor, 500 nodular hyperplasia were seen; 9 out of 17 had microscopically observable hepatomas versus 0 out of 20 in controls. No tumors were seen in the other groups (Ito et al., 1973). Other studies on mice have shown PCB induced hepatomas (U.S.EPA, 1980).

Kimbrough et al. (1975) fed female Sherman rats a diet of 0 or 100 ppm roclor 1260 for 91 weeks. The incidence of hepatic carcinoma in the rats was 26/184, while the incidence of carcinoma in the control group was 1/173. Neoplastic nodules were observed in 144/184 livers of treated rats; 0/173 nodules were observed in control rats.

Five week old male mice of the Balb/cJ strain were fed Aroclor 1254 at 0 or 300 ppm for 6 or 11 months (Kimbrough and Lindner, 1974). The incidence of hepatoma in mice treated with Aroclor 1254 for 11 months was 9/22, and 1/24 for mice treated for 6 months. No hepatomas were seen in either the 6 or 11 month control groups.

The National Cancer Institute (NCI, 1978) conducted a study in which 7-week old male and female F-344 rats were fed 0, 25, 50, and 100 ppm Aroclor 1254 for 105 weeks. Mortality of treated males was significantly higher than controls; this effect was not seen in treated females. Various tumors were seen in organs of treated rats, but these were not dose related. The incidence of tumors of the liver and gastrointestinal tract was not statistically significantly increased, however, the incidence of nodular hyperplasia was treatment related.

Liver sections from the NCI study were reexamined by Ward (1985). The combined incidence of hepatocellular adenoma and carcinoma was found to have been significantly increased in male treated rats, but not in females. When total incidence of hepatic adenoma and carcinoma from both sexes was combined, the incidence of tumors from treated groups was significantly greater than in controls (Table II).

In a study by Norback and Weltman (1985), weanling male and female Sprague-Dawley rats were exposed to Aroclor 1260 in the diet for a period of 24 months at a concentration of 100 ug/g. This diet was continued for 16 months followed by 50 ug/g for an additional 8 months. Afterwards a basal diet was fed until the 29th month. A partial hepatectomy was performed on a subgroup of treated rats. The treated male rats showed no significantly increased incidence of hepatocellular neoplasias, whereas female rats showed a significant increase in trabecular carcinoma and adenocarcinoma of the liver (18/47) over controls (0/49). The incidence of hepatocellular carcinoma in females was 24 out of 47 in treated rats and 0 out of 49 in controls.

In a study by Schaeffer et al. (1984), 100 ppm of Clophen A30 (similar to Aroclor 1242) and Clophen A60 (similar to Aroclor 1254) were added to the diets of 8 week old male Wistar rats. A total of 139 rats served as controls. After 114 weeks on the study, animals from each group were randomly sacrificed until the 119th week, at which time the study was concluded. No significant increase in tumor incidence was reported for rats treated with Clophen A30, only a significant increase in neoplastic nodules occurred. However with the Clophen A60 group there was a significant increase in both hepatocellular carcinoma (61/121) and neoplastic nodules (123/129) (Table II).

PCBs may also promote carcinogenic effects of other chemicals by inducing mixed function oxidases, which in turn metabolize precarcinogens to ultimate carcinogens. Ito et al. (1978) observed a pronounced increase in the incidence of preneoplastic nodules in N-2-fluoroacetamide treated rats. PCBs did, however, inhibit tumor formation in other models (U.S.EPA, 1980).

Table II

Incidence of Liver Tumors in Rats Induced by Polychlorinated Biphenyls^a

Dose Levels ^b		Responses		
Experimental	Adjusted	(# animals with tumor/# animals at risk)		
ppm	mg/kg/day	Male	Female	Combined
<u>Ward - Hepatocellular Adenoma or Carcinoma^c</u>				
0	0	0/24	0/23	0/47
25	0.532	1/24	0/24	1/48
50	1.064	2/24	3/24	5/48
100	2.128	7/24	2/24	9/48
<u>Kimbrough - Liver Neoplastic Nodules^d</u>				
0	0		0/173	
100	1.55		144/184	
<u>Kimbrough - Hepatocellular Carcinoma^d</u>				
0	0		1/173	
100	1.55		26/184	
<u>Schaeffer - Hepatocellular Carcinoma^e</u>				
0	0	0/109		
100	3.49	61/121		
<u>Schaeffer - Neoplastic Nodules or Hepatocellular Carcinoma^f</u>				
0	0	6/131		
100	3.49	123/129		

^a Data are taken from Ward (1985), a review paper on the NCI diet study; Kimbrough et al. (1975) and Schaeffer et al. (1984) diet studies.

^b Dose levels are converted from ppm to mg/kg per day by multiplying by a factor of 0.05 (Hartung et al., 1985). Doses are further multiplied by a factor of $(105/130)^4$, $(94/130)^4$ and $(832/7 \times 130)^4$ for the Ward, Kimbrough and Schaeffer studies, respectively, due to termination of the experiment before the animals have lived out their full life spans.

^c Number of animals at risk is the number of animals in the experiment initially.

^d Number of animals at risk is the number of animals examined.

^e Number of animals at risk is the number of animals alive at day 601.

^f Number of animals at risk is the number of animals alive at day 301, which is the time of the first response (301-400 days).

Incomplete evidence suggests that PCBs are carcinogenic to humans. Nine of twenty-two Yusho patients that died before 1974, died with malignant neoplasms. Industrial workers heavily exposed to Arochlor 1254 had an incidence of melanoma in two cases out of 31 workers. An incidence of 0.04 malignant melanomas would have been expected, so that the data are significant at the p 0.001 level (NCI, 1978). These workers were exposed to other chemicals, and this makes the association with PCBs quite speculative.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

The studies by Schaeffer et al. (1984) and Kimbrough et al. (1975), as well as the review of Ward (1985) were judged appropriate for risk assessment due to their durations and significant incidences of hepatocellular tumors in treated groups. Other studies were judged to be inappropriate due to their less than life-time exposure (Kimbrough and Lindner, 1976) or employed a variable dosing regimen (Norback and Weltman, 1985).

The study by Schaeffer et al. (1984) was selected for the determination of the MCL because it had the longest duration of exposure, and would provide the best estimate of lifetime exposure.

Calculation of the Health-Based Maximum Contaminant Level

The incidence of hepatic hepatocellular carcinomas in male rats obtained from Schaeffer et al. (1984) was fitted to the multistage model using an updated version of GLOBAL 82 by Crump (1985). All calculations were provided by K.S. Crump and Co. The multistage model is given by:

$$P(d) = 1 - \exp(-q_0 - q_1 d - \dots - q_k d^k),$$

$q_i \geq 0$, $i = 0, 1, \dots, k$, where d is dose, $P(d)$ is the lifetime probability of cancer at dose d and k , q_0, \dots, q_k are parameters. In practice, k is set equal to the number of dose groups less one.

Extra risk above background is defined as

$$[P(d) - P(0)]/[1 - P(0)],$$

for the multistage model. Extra risk may be interpreted as the probability of the occurrence of cancer at a dose d , given that no cancer would have occurred without any dose.

The bioassays from Ward (1985), Kimbrough et al., (1975) and Schaeffer et al., (1984) are lifetime diet studies; the doses are measured in ppm.

Doses in mg/kg body weight per day are derived from doses in ppm by the following conversion (Hartung et al., 1984):

$$\begin{aligned} \text{dose (mg/kg/day)} &= \text{dose (ppm)} \times 10^{-6} \times (17,500 \text{ mg/day}) / 0.35 \text{ kg} \\ &= \text{dose (ppm)} \times 0.05. \end{aligned}$$

In this equation, 17,500 mg/day represents the daily food intake of a rat, and 0.35 kg represents the weight of a rat.

The results are shown in Table II.

Parameters of the multistage model are estimated by the method of maximum likelihood. The likelihood method (Crump and Howe, 1985) is used to calculate confidence limits.

The upper 95% confidence limit on the slope, or potency (q_1^*) derived from the model is $0.245 \text{ (mg/kg/day)}^{-1}$. The dose to the test animal that represents 10^{-6} risk is $4.08 \times 10^{-6} \text{ mg/kg/day}$.

Animal-to-human extrapolation is based upon the assumption that both animals and humans are equally susceptible (in terms of extra risk) to the carcinogen when dose is measured in the same unit for both species (Crump and Howe, 1980).

In this report, the mg/m^2 body surface area per day will be used for animal-to-human extrapolation. When the surface area conversion basis is used, then the human dose (Dh) measured in mg/kg/day is given by

$$D_h = D_a (W_a/W_h)^{1/3},$$

where D_a is the animal dose (10^{-6} risk) W_a and W_h are the weights of animals and humans, respectively, measured in the same units. Thus

$$\begin{aligned} D_h (\text{mg/kg/day}) &= 4.08 \times 10^{-6} \text{ mg/kg/d} (0.35/70)^{1/3} \\ &= 6.976 \times 10^{-7} \end{aligned}$$

¹ Let W_a and W_h be in kg, and let S_a and S_h be the surface areas of animals and humans, respectively, in m^2 . Surface area is approximately proportional to body weight to the $2/3$ power; this means that $S_a = KW_a^{2/3}$ and $S_h = KW_h^{2/3}$ for some constant K . The animal dose $\text{mg/m}^2/\text{day}$ that is equivalent to D_a is therefore $D_a W_a / S_a = D_a W_a^{1/3} / K$. Under the surface area method for converting risk, this also represents the equivalent human dose in $\text{mg/m}^2/\text{day}$. Converting the units of this dose to mg/kg/day yields $D_h = (D_a W_a^{1/3} / K) (S_h / W_h) = (D_a W_a^{1/3} / K) (K W_h^{2/3} / W_h) = D_a (W_a / W_h)^{1/3}$.

The health-based maximum contaminant level (MCL) that would deliver the human dose is calculated by:

$$\text{MCL (ug/L)} = \frac{\text{Dh (mg/kg/d)} \times \text{Wh (kg)} \times 1000 \text{ (ug/mg)}}{\text{V (L/d)}}$$

where V = water volume consumed daily by human

$$\text{MCL (ug/L)} = 6.976 \times 10^{-7} \times 70\text{kg} \times 1000 \text{ (ug/mg)} / 2 \text{ L}$$
$$\text{MCL} = 0.024 \text{ ug/L}$$

As a result, the 95% upper bound on the 10^{-6} risk was determined to be 0.024 ug/L from the multistage model.

If the incidence of neoplastic nodules or hepatocellular carcinoma were combined from the Schaefer et al. (1984) study, the resulting MCL would be 0.005 ug/L.

The corresponding 10^{-6} risk level derived from the Kimbrough et al. (1975) and Ward (1985) was approximately twofold higher than from Schaeffer et al. (1984).

Assumptions and Uncertainty

Neoplastic nodules observed in several studies including Schaeffer et al. (1984) were not used in the calculations, since the pathologic status of these nodules is not clearly defined.

Calculation of the MCL was carried out for Clophen A60, although Clophen A30 was shown not to produce a significant amount of tumors. There are significant variations in the carcinogenic potency of PCB isomers, but there is little information to factor these variations into risk assessment. It is not practical to have MCLs for each PCB mixture so the most potent mixture was used for derivation of the MCL.

To convert the human dose in mg/kg body weight per day to ug/L drinking water concentration, the following assumptions are made.

1. The average body weight for humans is 70 kg.
2. Water consumption by a human is 2 L per day.

Conclusions

From this analysis it was derived that a lifetime exposure of 0.024 ug/L of PCBs should result in no more than 1 excess cancer in 10^6 individuals.

BIBLIOGRAPHY

- ACGIH. The American Conference of Governmental Industrial Hygienists. 1980. Documentation of threshold limit values. 4th ed. Cincinnati, Ohio. p. 486.
- Albro, P.W. and Fishbein, L. 1972. Intestinal absorption of polychlorinated biphenyls in rats. *Bull. Environ. Contam. Toxicol.* 8:26.
- Allen, J.R., Barsotti, D.A., and Corstens, L.A. 1980. Residual effects of polychlorinated biphenyls on adult nonhuman primates and their offspring. *J. Toxicol. Environ. Health* 6: 55-56.
- Allen, J.R., Barsotti, D.A., Lambrecht, L.K., and Van Millen, J.P. 1979. Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. *Ann. N.Y. Acad. Sc.* 320: 419.
- Allen, J.R., Carstens, L.A., and Baroliti, D.A. 1974. Residual effects of short-term, low-level exposure of non-human primates to polychlorinated biphenyls. *Toxicol. Appl. Pharmacol.* 30:440-451.
- Barsotti D.A. 1981. Gross, clinical and reproductive effects of polychlorinated biphenyls (PCBs) in the rhesus monkey. *Diss. Abstr. Int.* 41(10):3744-3745.
- Barsotti, D.A. and Allen, J.R. 1975. Effects of polychlorinated biphenyls on reproduction in the primate. *Fed. Proc.* 34: 338.
- Barsotti, D.A., Marlar, R.J., and Allen, J.R. 1976. Reproductive dysfunction in rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). *Food Cosmet. Toxicol.* 14: 99-103.
- Bowman, R.E. Heironimus, M.P., and Allen, J.R. 1978. Correlation of PCB body burden with behavioral toxicology in monkeys. *Pharmacol. Biochem. Behav.* 9: 49-56.
- Bruckner, J.V., Khanna, K.L., and Cornish, H.H. 1973. Biological responses of the rat to polychlorinated biphenyls. *Toxicol. Appl. Pharmacol.* 24: 434.
- Chase, K.H., Wong, O., Thomas, D., Berney, B.W., and Simon, R.K. 1982. Clinical and metabolic abnormalities associated with occupational exposure to polychlorinated biphenyls (PCBs). *J. Occup. Med* 24: 109-114.
- Chen, P. Wong, C.K., Rappe, C., and Nygren, M. 1985. Polychlorinated biphenyls, dibenzofurans and quarter-phenyls in toxic rice-bran oil and in the blood and tissues of patients with PCB poisoning (Yu-Cheng) in Taiwan. *Environ. Health Perspect.* 59: 59-66.

- Crump, K.S. 1986. Quantitative risk assessment for selected volatile organics in drinking water. Prepared for the Office of Science and Research, New Jersey Department of Environmental Protection by K.S. Crump and Co.
- Crump, K. and Howe, R. 1985. Review of methods for calculating statistical confidence limits in low dose extrapolation. In: Toxicological Risk Assessment. Clayson, D., Krewski, D., Monroe, I., eds. Volume I. CRC Press, Inc., Boca Raton, Florida.
- Dennis, D.S. 1976. Polychlorinated biphenyls in the surface waters and bottom sediments of the major drainage basins of the United States. Page 183. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Ill. EPA 560/6-75-004. Off. Tox. Subst. U.S. Environ. Prot. Agency, Washington, D.C.
- Fein, G.G., Jacobson, J.L., Jacobson, S.W., Schwartz, P.M., and Dowler, J.K. 1984. Prenatal exposure to polychlorinated biphenyl: Effects on birth size and gestational age. J. Pediatrics. 105: 315-320.
- Finklea, J., Priester, L.E., Creasons, J.P., Hauser, T., and Hammer, D.J. 1972. Polychlorinated biphenyl residues in human plasma exposure. A major urban pollution problem. Am. J. Pub. Health 62: 645.
- Fischbein, A., Wolff, M.S., Lillis, R., Thornton, J., and Selikoff, I. 1979. Clinical findings among PCB exposed capacitor manufacturing workers. Ann. N.Y. Acad. Sci. 320: 703-15.
- Goldstein, J.A., Hickman, P., Bergman, H., McKinney, J.D., and Walker, M.P. 1977. Separation of pure polychlorinated biphenyl isomers into two types of inducers on the basis of induction of cytochrome P-450 or P-448. Chem-Biol. Interact. 17: 69.
- Green, S. 1975. Lack of dominant lethality in rats treated with polychlorinated biphenyls (Aroclors 1242 and 1254). Food Cosmet. Toxicol. 13:507.
- Hartung, R., Dourson, M., and Hertzberg, R. 1984. Health risks from noncarcinogens for less than lifetime exposures. (Unpublished report).
- Howe, R. and Crump, K. 1982. Global 82: A computer program to extrapolate quantal animal toxicity data to low doses. Prepared for the Office of Carcinogen Standards OSHA, U.S. Department of Labor, Contract 41 USC242C3.
- IARC. International Agency for Research on Cancer. 1974. Monographs on the evaluation of carcinogenic risk of chemicals to man: some anti-thyroid and related substances, nitrofurans and industrial chemicals. IARC, Lyon, France. Vol. 7.

- Ito, N., Nagasaki, H., Arai, M., Sugihara, S., and Hirae, K. 1973. Histo-pathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. *J. Nat. Cancer Inst.* 51: 1637-1646.
- Ito, N., Tatematsu, M., Hirose, M., Nakanishi, K., and Muraski, G. 1978. Enhancing effects of chemicals on production of hyperplastic liver nodules induced by N-2 fluorenylacetylamide in hepactomized rats. *Gann.* 69: 143-144.
- Jelinek, C.F. and Corneliussen, P.E. 1976. Levels of PCBs in the U.S. food supply. In: *Natl. Conf. Polychlor Biphenyls*, Nov. 19-21, Chicago, Ill. EPA 560/6-75-004. *Off. Tox. Subst., U.S.EPA*, Washington, D.C.
- Kimbrough, R. and Linder, R. 1974. Induction of adenofibrosis and hepatomas of the liver in BALB/cJ mice by polychlorinated biphenyls (Aroclor 1254). *J. Nat. Cancer Inst.* 53: 547-552.
- Kimbrough, R.D., Squire, R.A., Linder, R.E., Strandberg, J.D., Montali, R.J., and Burse V.W. 1975. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. *J. Nat. Cancer Inst.* 55: 1453-1459.
- Kikuchi, M. 1984. Autopsy of patients with Yusho. *Am. J. Ind. Med.* 5: 19-30.
- Koller, J.D. 1977. Enhanced polychlorinated biphenyl lesions in Moloney leukemia virus-infected mice. *Clin. Toxicol.* 11: 107-116.
- Kunita, T., Hor, S., Obana, H., Otake, T., Nishimura, H., Kashimoto T., and Ikegami, N. 1985. Biological effect of PCBs, PCQs and PCBFs present in the oil causing Yusho and Yu-Cheng. *Environ. Health Perspect.* 59: 79-84.
- Kuratsune, M. 1972. An abstract of results of laboratory examinations of patients with Yusho and animal experiments. *Environ. Health Perspect.* 1: 129-136.
- Kuratsune, M., Yoshimura, T., Metzuzaka, J., and Yamaguchi, A. 1972. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. *Environ. Health Perspect.* 1: 119-128.
- Kutz, F. and Yang, H.S.C. 1976. A note on polychlorinated biphenyls in air. In: *Natl. Conf. Polychlor. Biphenyls*, Nov. 19-21, 1975, Chicago. Ill. EPA 560/6-75-004. *Off. Tox. Subst., U.S. EPA*, Washington, D.C. p. 182.
- Masuda, T., Kuroki, H., and Haraguchi, K. 1985. PCB and PCDF congeners in the blood and tissues of Yusho and Yu-Cheng patients. *Env. Health Perspect.* 59: 53-58.

- Matthew, H.B. and Anderson, M.W. 1975. Effect of chlorination on the distribution and excretion of polychlorinated biphenyls. *Drug Metab. Dispos.* 3: 371.
- Meigs, J.W., Alborn, J.J., and Kartin, B.L. 1954. Chloracne from an unusual exposure to Arcolor. *J. Am. Med. Assoc.* 154: 1417-1418.
- Nagayoma, J., Kuratsune, M., and Masuda, Y. 1976. Determination of chlorinated dibenzo furans in Kanechlos and Yusho oil. *Bull. Environ. Contam. Toxicol.* 15: 9-13.
- NCI. National Cancer Institute. 1978. Bioassay of Aroclor 1254 for possible carcinogenicity. CAS No. 27323-18-8, Technical Report Series, No. 38, NCI-CG-TR-38.
- NCI. National Cancer Institute. 1978. Bioassay of Arcolor (trademark) 1254 for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 38., Bethesda, MD.
- N.J.DEP. New Jersey Department of Environmental Protection. 1985. Results of initial testing for contaminants in public water supplies under assembly bill A-280. Office of Science and Research and Division of Water Resources, N.J. Department of Environmental Protection, Trenton, N.J.
- NIOSH. National Institute for Occupational Safety and Health. 1977. Criteria for a recommended standard...occupational exposure to polychlorinated biphenyls (PCB's). Rockville; MD: U.S. Department of Health, Education and Welfare. DHEW. Publ. NIOSH 77-225.
- Norback, D.H. and Weltman, R.H. 1985. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. *Environ. Health Perspect.* 59: 97-106.
- Pheng, P., Wong, C-K., Rappe, C., and Nygren, M. 1985. Polychlorinated biphenyls, dibenzofurans and quaterphenyls in toxic rice-bran oil and in the blood and tissues of patients with PCB poisoning (Yu-Cheng) in Taiwan. *Env. Health. Perspect.* 59: 59-68.
- Schaeffer, E., Greim, H., and Goessner, W. 1984. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. *Tox. Appl. Pharmacol.* 75: 278-288.
- Schoeny, R. 1982. Mutagenicity testing of chlorinated biphenyls and chlorinated dibenzofurans. *Mut. Res.*, 10:45.
- Smith, A.B., Schloemer, J., Lowry, L.K., Smallwood, A.W., Ligo, R.N., Tanaka, S., Strinaer, W., Jones, M., Herwin, R., and Glueck, C.J. 1982. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. *Br. J. Ind. Med.* 39: 361-369.

Takamatsu, M., Oki, M., Maeda, K., Inoue, Y., Hirayama, H., and Yoshizuka, K. 1985. Surveys of workers occupationally exposed to PCBs and Yusho patients. *Environ. Health Perspect.* 59: 91-97.

U.S.EPA. United States Environmental Protection Agency. 1980. Ambient water quality criteria for polychlorinated biphenyls. Office of Drinking Water, Criteria and Standards Division. Washington, D.C. Publication No. EPA 440/5-80-068.

U.S.EPA. United States Environmental Protection Agency. 1985. Polychlorinated biphenyls (PCBs) health advisory draft. Office of Drinking Water. September 30, 1985.

Ward, J.M. 1985. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. *Environ. Health Perspect.* 60: 89-95.

Wyndham, C., Devenish, J., and Safe, S. 1976. The *in vitro* metabolism, macromolecular binding and bacterial mutagenicity of 4-chlorobiphenyl, a model PCB substrate. *Res. Commun. Chem. Pathol. Pharmacol.* 15: 563.

Yamashita, F. and Hayashi, F. 1985. Fetal PCB syndrome: clinical features, intrauterine growth retardation and possible alteration in calcium metabolism. *Environ. Health Perspect.* 59: 41-46.

Yobs, A.R. 1972. Levels of polychlorinated biphenyls in adipose tissue of the general population of the nation. *Environ. Health Perspect.* 1: 79-82.