THE TOXICOLOGY OF PCB'S

An Overview with Emphasis on Human Health Effects
and Occupational Exposures

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I. INTRODUCTION

As a consequence of the Environmental Protection Agency (EPA) ban on further manufacture of polychlorinated biphenyls (PCBs) in 1977, occupational exposures to these compounds have been drastically reduced. However, significant exposures may remain for particular occupational groups. Utility workers, for example, may experience sporadic but potentially massive exposures when cleaning up spills, or when servicing and dismantling transformers and capacitors that still contain PCB fluid. Electricians, appliance service workers and firefighters also may have continued occupational exposure. The National Institute of Occupational Safety and Health (NIOSH) estimates that 12,000 workers have potential exposure as a result of current uses of PCBs (NIOSH, 1977). Despite the vast scientific literature on the toxicology of PCBs, the human health effects likely to result from such exposure remain illdefined.

The Hazard Evaluation System and Information Service (HESIS) has reviewed the literature on PCB toxicology in response to inquiries about worker health. Requests for information have come from unions and workers who handle PCB fluids in cleanup of spills, in maintenance work, and in transportation, storage and disposal of used equipment. Toxicology information has also been requested by medical professionals evaluating the clinical significance of PCB exposures, and public health officials who are attempting to set standards for occupational and environmental exposures. Our primary goal has been to review the data relevant to the human health effects of PCBs especially those resulting from occupational exposures. Since the published epidemiologic evidence is limited we have utilized animal toxicology studies where appropriate in anticipating potential biologic effects in humans. We have not attempted to summarize the extensive literature on PCB toxicology, but the reader is referred

to a number of recent reviews (DHEW, 1978; IARC, 1978; Fishbein, 1974; Kimbrough, 1974; EPA, 1977; Nelson, 1972; NIOSH, 1977).

II. GENERAL BACKGROUND INFORMATION

In all animal species that have been studied PCBs have a very low acute toxicity. They are readily absorbed across biological membranes, poorly metabolized and only very slowly eliminated. Because PCBs persist in the environment and accumulate in living tissue, they are concentrated ("biomagnified") in the food chain in a similar manner to other organochlorine compounds like DDT. Concern about exposure to PCBs has, therefore, focused on their resistance to biodegradation with the consequent potential for long-term or delayed health effects.

A number of published reports have established "background" levels of PCBs in the blood and tissues of human populations with no previous history of exposure. Surveys in various geographical areas have found detectable residues in blood, fat and mothers' milk. Measurable levels of PCBs are typically found in greater than 50% of subjects tested with maximum blood levels generally less than 20 ppb (Finklea, 1972). The levels reported from adipose tissue are typically somewhat higher, in the range of 1-2 ppm (Kutz, 1975). Residues of PCBs in human milk have ranged from 40-100 ppb in whole milk (New York State Health Council, 1977).

Two facts complicate the documentation of the human and animal toxicology of PCBs:

1. Commercial products are rarely single agents, but rather are complex mixtures of chlorinated biphenyls with different numbers and arrangements of attached chlorine atoms (see Figure I). The metabolism and toxicology of PCBs seem to vary with the percent of chlorination and with the isomeric structure of the PCB molecule.

2. All commercial products are potentially contaminated with chlorinated naphthalenes and polychlorinated dibenzofurans (PCDFs). The degree of this contamination varies with different commercial mixtures (see Figure III).

Contamination by dibenzofurans (PCDFs) is of particular concern because of the structural similarity of these compounds to the highly toxic dibenzodioxins (see Figure II). The pattern of observed effects in animals exposed to PCDFs closely resembles that seen following exposure to 2,3,7,8 tetrachlorodibenzodioxin (TCDD). In comparative animal studies the toxicity of PCDFs is much greater than the PCBs, particularly in the thymus, skin (acne), liver and hematopoetic system (Oishi et al., 1978; Moore et al., 1979). In addition, PCDFs are 1000 times more potent than PCBs as enzyme inducers (see Section VI).

Uncertainties in the analytic methods used for detection of PCBs must be considered when reviewing the published data on PCB toxicology: Monitoring PCBs in environmental or biological samples by gas-liquid chromatography/mass spectrometry (GC/MS) is made difficult by the presence of other chlorinated hydrocarbons (e.g., pesticides) which are commonly present at similar concentrations (Stalling et al., 1979). Because of the difficulties in the interpretation of GC/MS spectra and other methodologic problems including extraction and cleanup, the PCB levels reported from different laboratories may show considerable variation.

III. PHARMACOKINETICS

Absorption

There is relatively little information on the rate or degree of absorption of PCBs by any route for any species of animal. Since similar systemic toxicity has been observed in rodents after dermal, oral and inhalational adminstration of comparable doses, it is likely that PCBs are easily absorbed by all routes. The few quantitative measurements of relative absorption rates indicate that most, if not all, PCBs which contain six or fewer chlorine atoms are efficiently absorbed from the gastrointestinal (GI) tract (Albro and Fishbein, 1972; Van Miller et al., 1975; Matthews and Anderson, 1975).

Distribution, Accumulation (Mammals)

As with other heavily chlorinated chemicals the major storage tissue for PCBs is body fat. The concentration in adipose tissue is 10-1000 times that found in other tissues, both following single oral doses (Grant et al., 1971) and after chronic administration. (Curley et al., 1971) The lowest concentrations are found in whole blood and plasma where levels are usually several fold lower than in other tissues examined. This preferential distribution of PCBs into fat has been well documented after intravenous (i.v.) dosing in the rat (Lutz et al., 1977). Results are consistent with the high distribution coefficient of PCBs in fat and low perfusion of adipose tissue compared to skin, liver, muscle and blood (Anderson et al., 1977).

Two important pharmacokinetic questions cannot now be resolved on the basis of available data:

1. Does the concentration of PCBs reach steady state with constant exposure?

2. Will mobilization of adipose tissue after starvation or illness lead to a transient increase in PCB concentrations in blood and other tissues ?

Like most heavily chlorinated hydrocarbons the half-life of PCBs in animal tissue is quite long. In a chronic feeding study with Aroclor 1254 at 100 ppm in the diet of rats, a steady build-up of PCBs occurred in all tissues analyzed without a plateau level even after 240 days of treatment. By comparison, in a similar rat dietary study using DDT, plateaus in fat were attained after 90-140 days (Curley et al., 1971). In dairy cows a steady state was reached in 40-60 days (Fries, 1972), probably due to mobilization into fat micelles and secretion into milk. Thus, PCBs are unlikely to reach steady state levels in nonlactating animals; and fat mobilization or lactation may be expected to result in release of stored PCBs.

Transplacental Exposure, Secretion in Milk

Transplacental exposure of PCBs has been documented in mammals. Term fetuses taken from rats exposed to 10 mg/kg/day during days 7-15 gestation contained 0.63 ppm PCB, or about 1/60 the maternal dose. When the dose to the mother was increased five fold, the concentration in the fetuses increased two fold (Curley et al., 1973). The hyperpigmented babies observed in the Yusho incident (see Section VII) represent additional circumstantial evidence of transplacental passage of PCBs, although it is unclear whether these effects were related to PCB or to the PCDF contamination.

Secretion of PCBs into milk has also been observed. In mice, little passage of PCBs occurred across the placenta once PCBs had been sequestered into maternal adipose tissue, but they were readily transferred to suckling offspring through the milk (Vodicnik and Lech, 1980). These observations suggest that secretion of PCBs into milk may be quantitatively much more important as a source of exposure in newborns than is

transplacental passage. This has recently been documented in a prospective study of Japanese mothers and their infants (Hirokadzu and Ota, 1980).

Metabolism

PCBs are metabolized primarily by hydroxylation and conjugation with glucuronic acid. The primary site of biotransformation is assumed to be the liver, although no data is available currently on the possible role of peripheral metabolism, e.g., skin.

Many experimental feeding studies in both mammals and birds have shown an inverse relationship between percent chlorination and rates of metabolism. Less chlorinated PCBs are more readily metabolized than are more chlorinated ones, the rate of metabolism and excretion decreasing sharply as the number of chlorine atoms increases above five (EPA, 1977). The metabolism of the higher chlorinated biphenyls is also dependent on the position of chlorine atom substitution. The presence of two adjacent, unsubstituted carbon atoms is needed for the rapid enzymatic hydroxylation reaction (Jensen and Sundstrom, 1974). Since the more highly chlorinated biphenyls have a very much slower metabolic rate and longer half-life, they are more generally found as residues in human and animal tissues. This relationship alters with PCBs above 54% chlorination, presumably as a result of lower absorption from the gastrointestinal tract.

Arene oxide intermediates have been described in a major pathway of the metabolic transformation of PCBs by hepatic mixed function oxidases (Safe et al., 1975; Gardner et al., 1973). These intermediates are of particular concern since they are capable of direct interaction with DNA and may be the active form of carcinogenic polyacyclic hydrocarbons (Jerina and Daly, 1974). The PCB molecules which are more readily metabolized and excreted also are more likely to form these arene oxides. It does

not necessarily follow, however, that those compounds which persist in tissue and are more likely to be measured in population sampling, are less important in terms of their carcinogenic potential.

From the limited data available, it appears that significant differences exist between nonhuman primates and rodents in the metabolism and pharmacokinetics of PCBs. The marked variation observed in PCB toxicity between rodents and primates may be explained by such differences. Primates appear to be more susceptible to the toxic effects of PCBs than are rats or mice (see Section IV and Figure IV). When single doses of radiolabeled PCB were administered by gastric intubation to infant monkeys, the metabolites measured in urine, tissue (liver) and serum included hydroxylation products derived from arene oxide intermediates while in the rat, direct hydroxylation is the rule (Hsu et al., 1975).

There is virtually no pharmacokinetic data in humans. A few generalizations can be made, however, based on studies reporting PCB blood levels: the higher the exposure levels, the higher blood concentration of PCBs (Hara et al., 1975; Inoue et al., 1975; Karppanen and Lolho, 1973; Baker et al., 1980); and the higher the environmental concentration and/or the longer the period of exposure, the longer the blood levels of PCBs remain elevated (Hara et al., 1975; Baker et al., 1980). However, there are a few reports which are inconsistent with this latter trend (Bumgarrer et al., 1975; Hasegawa et al., 1972; Kitamura et al., 1973). PCB levels have also been correlated with race and geographic residence (NIOSH, 1977) and with age and dietary intake of fish (Kimbrough, 1980).

Comments

Certain generalizations can be made from the limited pharmacokinetic data that is available:

1. Absorption occurs by all routes (skin, GI, inhalation).
2. Distribution is primarily into fat.
3. Metabolism and excretion are dependent on specific molecular structure, varying inversely with percent chlorination.
4. Excretion is in general quite slow so that bioaccumulation occurs even at low exposure levels.
5. Transplacental transfer occurs but may be quantitatively less significant than secretion into milk.
6. Arene oxide metabolites are found in the metabolic transformation of PCBs. These compounds are highly reactive and may represent the active carcinogens (see Section V).
7. The relationship between percent chlorination and potency as carcinogen has not been established.
8. There are essentially no pharmacokinetic data in humans; it is not known, for example, if intermittent high doses are more or less hazardous than low level chronic exposures to the same total dose.

IV. ANIMAL TOXICOLOGY

Acute Toxicity

When given as a single dose, the acute oral LD_{50} of PCBs in rats, rabbits and mice ranges from 1-10 g/kg of body weight. According to the American Industrial Hygiene Association classification system for acute toxicity, PCBs are classified as "slightly toxic" (0.5-5 g/kg), or "practically nontoxic" (5-15 g/kg). There is some evidence that young animals are more sensitive than adults, and that females are more susceptible than males to the acute effects of PCBs (Kimbrough et al., 1978). In rodents, the acute oral toxicity appears to decrease with increasing chlorine content of the administered PCBs. This may be secondary to decreased absorption of the higher chlorinated compounds or to the differences in metabolic transformation previously discussed.

Although few clinical signs of toxicity have been reported in experimental animals, pathologic findings are extensively documented. Central Nervous System (CNS) depression (decreased pain response and diminished exploratory behavior), anorexia and oliguria followed by ataxia, coma and death have been observed in rats following acute administration of large doses of PCBs (Brackner et al., 1973). Consistent pathologic findings associated with death in rats, rabbits and guinea pigs include liver damage with fatty infiltration, centrolobular atrophy, and in some cases necrosis. Pathologic changes in other organs in these species are not often described, except for chloracne-like lesions which occur at the site of skin or intradermal application.

Comments

The low order of acute toxicity in experimental animals is consistent with the lack of acute effects observed in workers exposed to PCBs. Reported symptoms after occupational exposures include mild irritation of the skin and eyes at levels above 0.1 mg/m^3 with unbearable irritation occurring above 10 mg/m^3 (ACGIH, 1976). Systemic symptoms of nausea and headache have been reported but may be secondary to the solvents (such as trichlorobenzene) in the PCB mixtures.

Subacute and Chronic Toxicity

In contrast to the low order of acute toxicity, effects from chronic exposures to relatively low doses of PCBs have been consistently observed and are of far greater concern. These subacute effects show appreciable variation among species, but liver damage is again the prominent finding.

The major changes in rats fed Aroclor 1248, 1254, and 1262 at 100 ppm in their diet for six weeks included liver hypertrophy, marked fatty infiltration and degeneration of parenchymal cells. As in acute toxicity studies, PCB mixtures with lower chlorine content were more toxic (Allen and Abrahamson, 1973). In 8-12 month feeding studies increased serum lipids and focal areas of liver damage were observed (Allen et al., 1976; Kimbrough et al., 1972).

Nonhuman primates are more sensitive than rodents to the toxic effects of PCBs (see Table I and Figure IV). Adult female monkeys exposed to dietary levels of 2.5 ppm for 12 months (≈0.08 mg/kg/day) developed facial edema, alopecia, acne, gastritis with ulceration, anemia, hypoproteinemia and bone marrow hypoplasia. At 100 ppm (≈10 mg/kg/day) there was considerably more evidence of tissue damage than in rats,

including marked hepatic hypertrophy with ultrastructural abnormalities (Allen, 1975). Based on extrapolation from the Yusho data, PCBs may cause symptoms to humans at levels (0.2 mg/kg/day) which are comparable to the lowest doses which produce effects in nonhuman primates (see Table I).

Most of the animal data are derived from feeding or oral intubation studies. There are relatively few reports of dermal or inhalation experiments. Inhalation studies again revealed liver damage to be the prominent finding in rodents. For summary of inhalation data see the NIOSH criteria document, page 125 (NIOSH, 1977). Dermal toxicity studies in rabbits have produced skin lesions at the site of application as well as systemic effects including liver and kidney damage, thymic atrophy, lymphopenia and increased fecal porphyrins (Vos and Beems, 1971).

Comments

Liver damage, documented histologically, is the most consistent finding among the many laboratory animals species tested. Effects of low level chronic exposure does show appreciable variation among species, but liver damage has been observed in all species and is usually the most sensitive indication of PCB exposure. The fact that liver dysfunction has been inconsistently observed in humans may be an artifact of the relative insensitivity of the standard liver function tests (SGOT, SGPT) as compared to biopsy and histologic analysis (see Sec. VII, p. 25).

Reproductive Effects

Adverse reproductive effects of PCBs have been noted in many mammalian and avian species. The pattern of reproductive effects include alterations in estrus cycles, failure of implantation, increased frequency of spontaneous abortions, low birth weight offspring

and decreased post-natal survival. No specific teratogenic effects of PCBs have been observed in a variety of avian species. Transplacental effects, however, have been documented in both animals and humans (see Section VII).

PCBs given to mice for 10 weeks at dosage of 1.0 mg/kg/day lengthened the estrus cycle by more than two days and decreased the number of successfully implanted ova (Orberg and Kihlstrom, 1973). Similarly, mice that received PCBs as sucklings in a long-term transgenerational study showed subsequent alterations in estrus cycles, decrease in implantations, and when mated to each other (F1 studies), reduced number of offspring per litter (Kihlstrom et al., 1975).

In rats, studies suggest that reproductive effects of PCBs decrease as chlorination increases. No reproductive effects have been found with Aroclor 1260 (60 percent chlorination) at 1, 10, 100 ppm, but significant effects have been noted with Aroclor 1242 and 1254 (42 and 54 percent chlorination, respectively) at doses of 20 and 100 ppm. Aroclor 1260 began to exert toxic effects at doses of 500 ppm. Rats chronically fed from 20 to 100 ppm Aroclor 1242 and 1254 had reduced numbers of offspring. Surviving newborns showed increased mortality, with only 30 percent surviving to weaning. Five ppm of either Aroclor 1242 or 1254 produced no effects over two generations. Thus, the minimum effective doses ranged from 20 ppm for the lower chlorination mixtures to 100-500 ppm of the more highly chlorinated compounds (Keplinger et al., 1971; Linder, et al., 1974).

Evidence of adverse reproductive effects is also available for nonhuman primates. Rhesus monkeys fed 2.5 and 5.0 ppm Aroclor 1248 for 18 months in the diet showed changes in menstrual cycles in addition to other systemic signs of toxicity. Evidence was also obtained for frequent resorptions and spontaneous abortions following breeding

to normal males. In all, six infants were carried successfully to term out of 14 pregnancies. The offspring were of low birth weight and by two months began to show evidence of PCB toxicity, presumably from PCBs in the maternal milk; only three infants survived to six months. Behavioral tests in the three surviving animals showed marked deficits in several learning tasks, with increasing errors correlated with increasing body burdens of PCBs (Allen and Barsotti, 1976; Bowman et al., 1978; Barsotti et al., 1976).

The effect of PCBs on the male reproductive system is not known. There is one report of four male Rhesus monkeys exposed to 5.0 ppm Aroclor 1248 in the diet for 18 months. After 12 months, one of four animals developed clinical signs of PCB intoxication, showed marked sperm count depression and was functionally sterile. A testicular biopsy revealed a marked decrease in spermatogonia. A second biopsy one year after exposure showed complete recovery (Allen et al., 1979). PCBs are negative in the mouse sperm morphology assay (Heddle and Bruce, 1977).

Comments

PCBs show significant effects on reproductive competence in a variety of species. These effects increase in intensity with increasing dosage and decrease with increasing chlorination of the PCB isomers. PCBs do not appear to be mammalian teratogens. A reasonable explanation for most of the reproductive effects of PCBs could be based on their estrogenic activity (see below).

PCBs have been detected in human semen (Dougherty et al., 1980), but there have been no studies of semen quality in relation to PCB exposure in humans. The effects of PCBs on the male reproductive system in animals or humans has not been adequately

studied. The only other evidence to date on reproductive toxicity in humans come from the Yusho incident and is summarized in Section VII.

Other

1. Immunosuppressive Effects

A number of reports implicate PCBs as immunosuppressants (Fishbein, 1974). Lymphoid atrophy has been observed in rabbits, chickens and guinea pigs. Suppression of humoral immune responses to several antigens was observed in rabbits and guinea pigs, and decreased cell-mediated immune response followed PCB exposure in guinea pigs. A decreased tolerance to hepatitis virus was seen in ducklings without apparent intoxication. In monkeys exposed transplacentally and through contaminated milk, the lymph nodules of the spleen were extremely small and without germinal centers (Allen and Barsotti, 1976); morphologic changes were indicative of reduced immunologic competence.

2. Endocrine Effects

Subcutaneous administration of Aroclor compounds with lower chlorination produced an estrogenic effect on the rat uterus which was not shown with Aroclors of higher chlorination (Bitman and Ceal, 1970). Female monkeys fed Aroclor 1248 for six months showed an increase in concentration of urinary ketosteroids and a prolongation of their menstrual cycles with increased bleeding (Barsotti et al., 1976). Antiandrogenic effects have been described in birds although the mechanism is not clear. It may be secondary to an increased rate of androgen metabolism in the liver by induction of microsomal enzymes (see Section VI), or by virtue of PCBs exerting estrogenic effects.

Comments

The effect of PCB exposure on immune and endocrine system function has not been carefully studied in humans, so the relevance of these animal observations to human health remains unknown. There is one cross-sectional study of occupational exposure to PCBs which will include analysis of serum hormone levels and urinary metabolites, but results have not yet been published (Selikoff et al., in progress).

V. CARCINOGENICITY/MUTAGENICITY

Carcinogenicity

Several PCB mixtures are clearly carcinogenic in rodent bioassays, producing liver tumors (hepatocellular carcinomas). Kanechlor 500 and Aroclor 1254 are carcinogenic in male mice (Ito et al., 1973; Kimbrough and Linder, 1974); and Aroclor 1260 is carcinogenic in separate studies in two strains of female rats (Kimbrough et al., 1975; Norback et al., 1980). In addition, a purified component of a PCB mixture, 2,4,5,2',4',5' -hexachlorobiphenyl, has recently been found to be carcinogenic in female rats, causing hepatocellular carcinomas (Norback et al., 1980).

Because high doses of PCBs are known to cause extensive injury to liver tissue it is important to consider the dose levels at which liver carcinomas were produced in the rodent bioassays. In two studies in rats, significant increases in hepatocellular carcinomas were present at doses which did not produce gross histologic changes. Hepatocytes were somewhat enlarged (probably due to microsomal enzyme induction), but no extensive fatty infiltration or necrosis occurred, as was characteristic of bioassays at higher dose levels (Kimbrough et al., 1975).

Test Results

1. Mice (Male)

   A. Kanechlor 300, 400, and 500 fed to groups of 12 eight-week-old male mice at 100, 250, and 500 ppm in the diet for 32 weeks produced hepatocellular carcinomas in 5 of 12 survivors in the high dose group fed Kanechlor 500. The remaining 7 mice in this group had nodular hyperplasia (neoplastic nodules). No metastases or other tumors were

present in this or other dosed groups. The control group (6 mice) was likewise tumor-free (Ito et al., 1973).

B. Aroclor 1254 administered to groups of 50 five to six-week-old male BALB/cJ mice at dietary levels of 0 or 300 ppm (about 50 mg/kg body weight during the exposure) for 11 months produced neoplastic nodules (hepatomas or hyperplastic nodules) in 9 of 22 survivors in the dosed group. Other liver lesions (adenofibrosis) were present in all 22 survivors. Additional morphological changes in the livers of these animals included pleomorphism and areas of necrosis. Such changes and tumors were absent among survivors (24) in the control group (Kimbrough and Linder, 1974).

2. Rats

A. Kanechlor 400 administered to ten-week-old Donryu rats (10 males and 10 females) at dietary levels which varied from 40-600 ppm during the 400-day study produced liver tumors (multiple adenomatous nodules) in 6/10 treated female rats. Such lesions were absent from the controls (5 males and 5 females) and the treated males (Kimura and Baba, 1973).

B. Kanechlor 300, 400, or 500 administered to groups of 30 eight-week-old male Wistar rats at dietary levels of 0, 100, 500, or 1000 ppm produced increases in the incidence of cholangiofibrosis at the highest dose level of all Kanechlors (2/15, 2/10, and 4/13, respectively). All three compounds also produced hepatic nodular hyperplasia, the incidence of which increased with dose and extent of chlorination (Kanechlor 300 at

100 ppm: 1/22; Kanechlor 400 at 100 ppm: 2/16, and 1000 ppm: 3/10; Kanechlor 500 at 100 ppm: 3/25, at 500 ppm: 5/16, and at 1000 ppm: 5/13); (Ito et al., 1974).

C. Aroclor 1260 administered to groups of 200 three to four-week-old female Sherman rats at 0 and 100 ppm in the diet (varying between 5-10 mg/kg body weight during the 21-month exposure) produced at 23 months among the dosed survivors clearly significant increases of hepatocellular carcinomas (controls 1/173; dosed group 26/184) as well as neoplastic nodules (hyperplastic nodules: controls 0/173; dosed group 146/184). The incidences of nonhepatic tumors did not differ between the dosed and control groups (Kimbrough et al., 1975).

D. Aroclor 1254 administered to groups of 24 eight-week-old Fisher 344 rats of either sex at dietary levels of 0, 25, 50, or 100 ppm for 105 weeks was not carcinogenic to any of the treated groups under the test conditions. It is important to note that two of the dose levels used were lower than those which produced a positive response in Sherman rats. Rare adenocarcinomas and carcinomas of the gastrointestinal tract appeared in both sexes and may be related to the administration of the PCBs (males: historical controls 6/600, dosed group 2/24). In addition a high incidence of hyperplasia was present among the dosed groups (males: controls 0/24, low-dose 5/24, mid-dose 8/24, high-dose 12/24; females: controls 0/23, low-dose 6/24, mid-dose 9/22, and high-dose 17/24); (NCI, 1978).

E. Aroclor 1260 administered to groups of 50 male and female Sprague-Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, causing significant increases in liver hepatocellular carcinomas (Norback and Weltman, 1980).

F. A purified component of a PCB mixture, 2,4,5,2',4',5'-hexachlorobiphenyl administered to groups of 50 male and female Sprague-Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, producing an increased incidence of liver hepatocellular carcinomas among the dosed animals (Norback and Weltman, 1980).

Mutagenicity

PCB mixtures have not been observed to have mutagenic activity nor to measurably affect chromosomes in repeated studies using a variety of in vitro or in vivo test systems Evidence of genetic damage from PCBs in laboratory test systems including chromosomal aberrations, nondisjunction, loss of sex chromosomes or increased frequency of sister chromatid exchange has not been observed. Report of a weak effect of Aroclor 1221 and of a stronger effect of 4-chlorobiphenyl in Salmonella using PCB-induced rabbit liver homogenate as a liver activation system appears unfounded (Wyndham et al., 1976). Further attempts to repeat these results have been unsuccessful using a variety of Salmonella tester strains and liver activation systems (Katzenellenbogen and Ames, 1980; Safe, 1978).

However, PCBs belong to the class of heavily chlorinated animal carcinogens, most of which are not positive in short-term tests for mutagenicity. Examples in this class include dieldrin, chlordane, kepone, mirex, TCDD*, chloroform, and carbon tetrachloride.

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* TCDD: Tetrachlorodibenzodioxin

Whether this is because the in vitro metabolic activation systems do not produce the same spectrum of metabolites that occur in vivo or because heavily chlorinated compounds such as PCBs are carcinogenic by nonmutagenic mechanisms is not known at this time.

Validation of the carcinogenic effects in rodents is provided by a positive cell transformation assay using C3H10T1/2 clone eight mouse fibroblast cells in culture by two separate PCB mixtures (Aroclor 1254 and 1260) and a purified component 2,4,5,2',4',5'-hexachlorobiphenyl (Norback and Weltman, 1980).

Comments

A wide variety of PCB mixtures have been subjected to rodent cancer bioassays and to numerous in vitro and in vivo short-term tests for mutagenicity. Several of these PCB mixtures are carcinogenic. None of the PCB mixtures are active in short-term tests for mutagenicity, a finding that holds true for most heavily chlorinated carcinogens. However, substantial confirming evidence for carcinogenicity is provided by positive cell transformation assays using these same PCB mixtures. Thus, under OSHA published criteria, PCB mixtures should be considered Category I* carcinogens. Both IARC (IARC, 1978) and EPA (EPA, 1978) have concluded that based on available animal data PCBs should be considered as potential human carcinogens.

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* Category I: Human evidence or two positive mammalian bioassays or 1 positive mammalian bioassay with supporting results in short-term tests.

Category II: One positive mammalian bioassay. (Source: Occupational Health and Safety Letter Vol. 9, No. 24 November 8, 1979)

VI. BIOCHEMICAL EFFECTS OF PCBs

Enzyme Induction

The principal biochemical effect of PCBs is the stimulation and induction of certain enzyme systems. Enzyme induction occurs in both the microsomal monooxygenase or cytochrome P-450 system and the aryl hydrocarbon hydroxylase or cytochrome P-448 system, and it has been observed in both man and experimental animals. Induction is not restricted to the liver. It occurs in numerous other organs including kidney, adrenal, lung, gut, skin, and testes. Fetal enzyme induction may occur via transplacental exposure, and induction may also occur by exposure to contaminated milk (Alvares and Kappas, 1975).

Identification of structure-activity relationships for enzyme induction is difficult because of the large number of isomers in commercially prepared PCBs and because all commercial products contain trace amounts of polychlorinated dibenzofurans (PCDFs) which are orders of magnitude more potent as enzyme inducers than PCBs (Matthews et al., 1978).

In early studies using commercial Aroclors, potency for enzyme induction was found to be dependent on chlorination of the PCB mixture. Later, when purified isomers were tested, potency was found to vary with the position of chlorine atom substitution (Ecobichon and Comeau, 1975; and see Section III). Since rate of metabolism is also known to vary with isomeric configuration of the PCB molecule, it may be that potency for enzyme induction is simply a function of the relative rate of metabolism and excretion.

The enzyme induction properties of PCBs are utilized in the metabolic activation system of in vitro bioassays for mutagenicity. It is unlikely, however, that enzyme induction would consistently enhance the effects of carcinogens or pro-carcinogens: it might function synergistically to activate a chemical, but they also might function to deactivate reactive carcinogens. Both phenomena have been observed in rodent cancer bioassays.

Porphyria

Porphyria cutanea tarda (PCT) in humans is an acquired defect in hepatic porphyrin metabolism characterized by uroporphorinuria, photosensitivity and mechanical fragility of the skin. PCT can be produced experimentally by a number of drugs, including tetrachlorodibenzodioxins and PCBs. All of these agents have the ability to stimulate the activity of 2-aminolevulinic acid (ALA) synthetase which is the initial enzyme in the heme synthetic pathway.

Experimental hepatic porphyria was observed in Sherman rats exposed to Aroclor 1254 in the diet. At doses of 100 ppm the animals became porphyric after a delay of approximately 2-4 months. The porphyria resembled hexachlorobenzene poisoning and human PCT (Goldstein et al., 1975).

In chronic feeding studies ALA-synthetase induction occurs after rats have become porphyric, although with large single doses the enzyme induction is seen almost immediately after dosing the animals (Goldstein et al., 1975).

It has not been established whether only certain isomers in the PCB mixtures or

contamination with PCDFs is responsible for the production of hepatic PCT. Porphyria has not been reported in humans exposed to PCBs.

Comments

Enzyme induction has two important implications for human health:

1. the occurrence of disease secondary to the increased metabolism of endogenous or exogenous substances, and
2. the interference with medical therapy due to increased metabolism of administered drugs.

PCBs are more potent enzyme inducers than phenobarbital, a drug that occasionally causes clinical problems due to its enzyme inducing effects. While the effects of phenobarbital decline after administration ceases, enzyme induction from PCBs persists long after cessation of exposure.

VII. HUMAN TOXICOLOGY AND EPIDEMIOLOGY

Few good epidemiologic studies of the health effects of PCBs are available. Most studies reported in the literature have been characterized by one or more of the following shortcomings:

1. small study populations,
2. lack of accurate exposure data,
3. simultaneous exposure of workers to other potentially harmful chemicals,
4. lack of control for confounding variables, such as alcohol consumption, and
5. inability to separate PCBs from contaminants and/or difficulty in comparing PCBs manufactured by different firms.

In spite of these problems, some health effects have been consistently reported in studies of workers occupationally exposed to PCBs. In addition, a large-scale poisoning which resulted from ingestion of PCB/PCDF-contaminated rice oil has been well documented and resulted in multiple signs and symptoms attributable to PCBs and/or PCDFs.

The health effects identified in a review of the epidemiologic literature are summarized below, and Table II briefly describes the major epidemiological studies from 1954 through 1980.

Dermatologic Changes

Chloracne, contact or allergic dermatitis, and brown chromodermatosis have been consistently reported in studies of workers exposed to PCBs (Hara et al., 1975; Hasegawa et al., 1972; Inoue et al., 1975; Kitamura et al., 1973; Baker et al., 1980; Meigs et al., 1954; Ouw et al., 1976; Schwartz, 1936).

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Systemic Symptoms

Nausea, digestive disturbances, headaches, upper respiratory problems, and persistent body odor have been reported as a result of occupational exposures (Ouw et al., 1976; Schwartz, 1936; Warshaw et al., 1979).

Liver Damage

Abnormal liver function tests have been reported in a number of occupational studies and clinical hepatitis was observed in the Yusho epidemic. However, some of the earlier investigations reporting abnormal liver function did not control for exposure to additional chemicals, previous medical history or drinking pattern and some of the marginal differences observed could have been related to these confounding variables.

More recently, Fischbein et al., (1979) found no significant differences in LFTs between capacitor manufacturing workers with low level chronic exposure and nonexposed controls. However, in a cross-sectional survey by Maroni et al., (1981 a & b) abnormal LFTs were observed and seemed to correlate with serum PCB levels. With the exception of a few cases of chloracne, these workers had no other symptoms, signs or laboratory abnormalities.

Yusho (Japanese word translated as "oil disease")

Both dermal and systemic health effects are well documented in the epidemiologic study of a poisoning epidemic in Japan caused by ingestion of contaminated rice oil in 1968 (Higuchi, 1976; Kuratsune et al., 1972).

It is not clear how much the health effects observed in Yusho victims can be extrapolated to occupational exposures for the following reasons:

1. The average amount of PCB (Kanechlor 400) ingested was estimated to be 2 grams and the minimum, 0.5 gram (Kuratsune et al., 1972). This is a higher dose than has been reported in most occupational exposures. In addition, the PCBs were ingested as opposed to inhaled or skin-absorbed as is the case with occupational exposures.

2. The contaminated oil contained "used" Kanechlor 400, the exact chemical compositon of which is unknown.

3. Frying of foods with the rice oil could have produced new compounds which may have altered the toxicity of the PCBs or the toxicity of possible contaminants.

4. Yusho oil was shown to contain high concentrations of dibenzofurans.

5. Reported concentration of PCBs in the oil may not have been accurate enough to permit a rigorous quantitative analysis since the methods for estimating PCBs in foods were not fully developed at the time.

Clinical features of the Yusho patients are listed in Table III. The Yusho incident is also important because it clearly documents the potential for reproductive and transplacental effects in humans.

A study was made of the 13 infants of 11 mothers affected by Yusho and of 2 unaffected wives of patients: 2 of the Yusho mothers had stillbirths; 10 of the babies had transient greyish or dark-brown pigmentation of the skin, and 5 had similar pigmentation of the gingiva and/or nails; increased ocular discharge was present in 9; and 12 of the 13 infants were small when compared with the national average (Funatsu et al., 1972; Kikuchi et al., 1969; Kuratsune, 1976; Taki et al., 1969). Babies born to patients even 3 years after severe PCB exposure tended to show pigmentation of the skin on the back and the gingiva, although the degree of pigmentation was less than that of babies born to the same mothers up to one year after the poisoning (Kuratsune, 1976).

Congenital abnormalities have also been observed in PCB-intoxicated infants. In the population of 13 offspring of Yusho mothers, premature eruption of teeth was observed in 2 cases, and larger than normal frontal and occipital fontanelles, exophthalmos and the persistence of an abnormally wide sagittal suture were observed in 3 others. No other gross malformations were reported nor was any relationship between dose and outcome considered (Funtasu et al., 1972).

Mothers' milk contaminated with PCBs also appears to be a source of exposure for infants: one baby showed signs of poisoning even though the mother had ingested the contaminated rice oil only after the baby was delivered. The infant began to show signs of PCB intoxication after 3-4 months of breast feeding (Kuratsune, 1972; Yoshimura, 1974).

Neurotoxicity

Paresthesias were reported in over 30% of Yusho patients (see Table III). In the Yusho epidemic more detailed neurologic examinations were performed in 21 cases admitted to a university hospital in northern Japan. Ten of the patients complained of numbness or pain in the distal extremities, and in five cases decreased pain, touch and temperature sensations were observed. Sensory conduction velocity in sural and radial nerves was below normal in 6 of 10 individuals with neuropathic symptoms (Murai and Kuroiwa, 1971).

A decrease in amplitude of muscle action potential evoked by nerve stimulation, and a decrease in sciatic nerve conduction velocity has been reported in rats intoxicated with tetrachlorobiphenyl. Thus, PCBs can affect peripheral nerve function in both

humans and experimental animals, but these have been reported only at doses which cause other systemic signs of poisoning.

Cancer

There is too little epidemiological evidence available yet to evaluate the potential of PCBs as human carcinogens (Bahn et al., 1980; Brown and Jones, 1980). A follow-up of the Yusho patients through 1977 has reported 51 deaths (31 with cause of death confirmed) of the 1,665 identified victims. There were 11 deaths from neoplasms, or 35.4% of the total. While this rate is higher than the 21.1% in the population of the same prefecture in 1977, these data were not age-adjusted. No particular site was elevated, and there were no deaths from malignant melanoma, a tumor previously suspected to be linked to PCB exposure (Bahn et al., 1976). Two liver cancers and two lung cancers were reported but smoking and drinking patterns were not available (Urabe et al., 1979).

A retrospective cohort mortality study of 2,567 workers in two capacitor manufacturing plants was recently completed by NIOSH. The report did not find any statistically significant SMR for any cause of death among exposed workers. Deaths from liver cancer, cirrhosis of the liver and rectal cancer were slightly higher than expected, though these excesses were not statistically significant and no information was available on medical histories, drinking patterns, etc. There was no relationship between increased mortality from all causes of cancer, rectal cancer or liver cancer, and length of exposure to PCBs. Limitations in the study design, however, might have obscured a true association. In particular, there was a relatively small sample followed over time thereby limiting the statistical power of this study. Second, there were on the average

only 15.19 years of follow-up for each exposed worker in the study. Usually the latent period between exposures and deaths from cancer is longer.

Third, exposure to PCBs was quantified for March 1977 only; there was no data on actual PCB exposures during the time when most of the population at risk was working with PCBs.

Finally, over 50% of the sample has exposure to PCB for only two years or less.

Ongoing Occupational Studies

Two additional cohort mortality studies are currently underway. The first is a mortality survey of the entire workforce employed between 1952-1957 at the largest United States' facility that manufactured capacitors and transformers. There is detailed information available on exposure levels in the plant. While the duration from onset of exposure is shorter than optimal (only 25 years in some cases), the information will at least give data on the short-term mortality experience of a heavily exposed occupational group (Selikoff et al., in progress).

The second is a similar occupational mortality study, also of workers exposed in capacitor and transformer manufacturing. Over 2,000 workers have been identified for this study but no further details are yet available (Bertazzi et al., in progress). One case control study is currently being conducted to assess whether there is excess risk of malignant melanoma among PCB-exposed workers. This data will not be available until March, 1982 (Bahn et al., 1976).

There is also one cross-sectional clinical field survey of 326 capacitor manufacturing workers at two sites, encompassing a total workforce of 800 (Fischbein et al., 1979). Exposures were classified as none, low, medium, and high based on job description at the time of the survey (1975). Researchers were able to identify the PCBs used and had some data on environmental air levels in the plants. A number of parameters were measured, including complete history and physical examinations, SMA panels and pulmonary function tests. Results have been published on respiratory function (Warshaw et al., 1979) and general signs/symptoms, and results of serum lipids, endocrine function and dermatologic findings are forthcoming. To date, the only positive association involves dermatologic signs and symptoms.*

Further investigations of the effects of PCB exposure on serum lipids have been done in both occupational and general environmental exposure settings. Smith et al., (1978), reported some statistically significant differences between exposed and nonexposed workers at two sites. They reported higher serum triglycerides and lower levels of high density lipo-proteins in the exposed group. Whether the magnitude of the difference is biologically significant is not clear from this study. For example, the nonexposed group at site #1 compared to the nonexposed group at site #2 showed a greater difference than the exposed and nonexposed comparison at either site. In another study (Baker et al., 1980) workers and community residents with exposure to fertilizer

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* Warshaw et al. (1979) concluded that there was also an association between PCB exposure and impaired pulmonary function (restrictive pattern). However, there were major methodologic problems with the data: the particular spirometer used (heated wire flow sensor) is notoriously inaccurate; it was not possible to link exposure data with particular PFT results; there was no information on race, and finally the magnitude of the observed effects was low and no statistical comparisons were done with nonexposed controls.

made from sewage sludge contaminated with PCBs were studied. Plasma triglyceride levels were found to increase significantly with serum PCB concentration (both in drinkers and nondrinkers), and the authors concluded that PCBs may alter lipid metabolism at levels of exposure and bioaccumulation insufficient to produce other identifiable signs of toxicity.

Comments

Although many problems have been identified in the studies evaluating the health effects of PCBs, it is clear that occupational exposure, at a minimum, can produce dermatologic effects. The long half-life of PCBs and their bioaccumulation in various human tissues leaves open the possibility of substantial chronic and delayed effects analogous to those seen in animal bioassays. These effects have only recently begun to be studied in a rigorous manner, and although the epidemiological evidence is neither complete nor entirely consistent there can be no question of the necessity to protect the worker from exposure.

VIII. MEDICAL SURVEILLANCE AND BIOLOGIC MONITORING

Medical surveillance and biologic monitoring are of limited usefulness in predicting health hazards if dose-response relationships are not known. This certainly is the case with PCBs. Based on animal toxicology, there are many suspected adverse effects of PCBs which might result from exposure in occupational settings, but very few have been documented well enough to give even rough estimates of "no-effect" or "safe" levels. A large percentage of nonoccupationally exposed people have detectable PCB levels in body fat, blood and milk. However, any attempt to estimate an adverse health effect associated with increases above this background level necessarily involves extrapolation from animal data and, therefore, is subject to considerable error, especially when the marked variation in sensitivity of various animal species is appreciated. Furthermore, not enough is known regarding the relative dose-response characteristics of the various documented effects (e.g., liver damage, skin changes) to state that in the absence of a particular sign, symptom or laboratory abnormality, the risk of long-term effect (cancer, reproductive toxicity) will be negligible (see Table I).

For the clinician confronted with a worker who has a history of exposure to PCBs the approach to management cannot be easily outlined. Given the current analytic methodology, residues can be measured in blood or tissue in the ppb range and compared to background; but assigning a health risk to a given level is virtually impossible, especially given the lack of pharmacokinetic data. Often patients are being evaluated after a considerable lag period (years) since last exposure occurred and extrapolation to peak blood levels is not possible. In fact, it may be that residue levels bear little relationship to the health risk. For example, the lower chlorinated compounds may be more toxic but they are more rapidly metabolized and excreted and, therefore, less likely to persist in blood or fat. Further, with the possible exception of chloracne,

the presence of specific signs, symptoms or laboratory abnormalities is very difficult to definitely relate to PCB exposure in any given patient.

Given these uncertainties and the potential for serious health effects, the approach to monitoring should emphasize environmental sampling and every attempt should be made to minimize exposure by engineering controls or personal protective measures in those settings where occupational exposure still occurs (e.g., utility repair workers). Biologic monitoring may be used to assess the effectiveness of environmental control, but it is really best utilized within a specific research protocol and probably has little value in the routine work-up of individual patients.

SUMMARY AND CONCLUSIONS

PCBs have low acute toxicity but are of public health concern because of their persistence in the environment and in human tissues and their demonstrated potential for chronic or delayed toxicity. They are potent inhibitors of reproductive function in both rodents and nonhuman primates and are positive in animal cancer bioassays. As potent inducers of hepatic enzyme systems, PCBs may have additional unpredictable long-term health effects.

Some of the conflicting reports in the toxicology literature are undoubtedly related to the variable composition and trace chemical contamination of the tested mixtures. Occupational and environmental exposure is usually to those mixtures; but if we are to accurately assess the associated health hazards, further animal studies are needed which carefully define the toxicology of the individual agents.

Epidemiologic studies of occupational exposures to PCBs to date have failed to detect serious adverse effects but are considered insufficient, and further studies are clearly needed. Of particular interest is the continued exposure among utility workers. Because of the potential ability to cause cancer and other long-term adverse effects such as infertility and hepatic injury, human exposure to PCBs should be kept to the lowest level technically possible. The persistence of PCBs in the body and the irreversibility of some of its effects make it necessary to act now, rather than to wait until more definitive data are available.

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TABLE I

DOSE-RESPONSE FOR ANIMAL TOXICOLOGY

Species	Age	Agent	Route	Dose mg/kg/day	Duration	Total Dose mg/kg	Effect	References
Rat	Adult	Aroclor 1254, 1260	Oral	4,000 - 10,000	Single Exposure	-----	LD_{50}	Kimbrough et al., 1978
Rat	Weanling	Aroclor 1254, 1260	Oral	1,700 - 1,300	Single Exposure	-----	LD_{50}	Kimbrough et al., 1978
Rat	Adult	Aroclor 1248, 1254, 1262	Oral	50	6 weeks	2100	Liver hypertrophy, fatty infiltration	Allen & Abrahamson, 1973
Rat	Weanling	Aroclor 1242, 1016	Oral	3.9-6.6	6 months	700-1200	Fatty liver	Burse et al., 1974
Rat	Adult	Aroclor	Oral	100	7-15 day gestation	700	↓survival - offspring no terata.	Linden et al., 1974
Rat	Adult	Aroclor 1260	Oral	25.0	2 months prior to mating	1500	↓litter size ↓survival offspring	Linden et al., 1974
Rat	Adult	Aroclor 1254	Oral	5.0	2 months prior to mating	300	↑mortality - offspring ↓mating behavior - offspring	Linden et al., 1974
Rat	Adult	Kaneclor 500	Oral	1.0	Day 8-14 or 15-21 gestation	6.0	↓various learning assays offspring	Shiota, 1976
Mice	Adult	"PCB's"	Oral	7.0	4 weeks starting at birth	200	↓implantations, litter size-offspring; changes in estrous cycle-offspring	Kihlstrom et al., 1975
Mice	Adult	Clophen A60	Oral	1.0	"chronic"	Unknown	lengthened estrous cycles ↓implantations	Oberg & Kihlstrom, 1973
Monkey	Adult	Aroclor 1248	Oral	10	4 weeks	840	weight loss, alopecia, facial edema, eye discharge	Allen, 1975
Monkey	Adult	Aroclor 1248	Oral	3.3	1 month	100	liver abnormalities (histological)	Allen, 1975
Monkey	"young"	Aroclor 1242	Oral	0.1-10	9 months	27-2700	death, gastric ulceration, facial edema, thymic atrophy	Allen, 1975
Monkey	Adult	Aroclor 1248	Oral	0.08-0.17	1 year	29-62	facial edema, alopecia acne, ↓fertility, irregular menses, ↑early abortions- offspring: ↓weight, head circumference, (detectable PCB's in tissue)	Allen, 1975
Rats	Adult	Aroclors	Dermal	≈100	25 days	2500	slight Δ's- liver histology	Miller, 1944
Guinea pig	Adult	Aroclors	Dermal	≈70	Single Exposure	----	death -- delayed up to 21 days with liver atrophy	Miller, 1944
Rabbit	Adult	Aroclor 1260	Dermal	≈20	38 days	760	skin, liver and kidney damage	Vos & Beems, 1971
Rat, Mouse, Guinea pig, and cat	Adult " "	Aroclor 1254 " "	Inhal. " "	2.5 *	17 weeks	450	microscopic liver Δ's	Treon, 1956
				0.7 *	31 weeks	217	reversible liver Δ's	Treon, 1956
Mice	8 weeks	Kaneclor 500	Oral	50	32 weeks	11.2**	↑hepatocellular carcinomas (control 0/6; dosed 5/12) ↑neoplastic nodules (control 0/6; dosed 7/12)	Ito et al., 1973
Mice	5 weeks	Aroclor 1254	Oral	50	46 weeks	16.1**	↑neoplastic nodules (control 0/24; dosed 9/22)	Kimbrough & Linden, 1974
Rats	4 weeks	Aroclor 1260	Oral	10	21 months	6.3 **	↑hepatocellular carcinomas (control 1/173; dosed 146/184) ↑neoplastic nodules (control 0/173; dosed 26/184)	Kimbrough et al., 1975
Rats	8 weeks	Aroclor 1260	Oral	10	104 weeks	7.2 **	↑hepatocellular carcinomas (unpublished, 1980)	Norbach et al., 1980
Rats	8 weeks	2,4,5,2',4',5' hexachlorobiphenyl	Oral	10	104 weeks	7.2 **	↑hepatocellular carcinomas (unpublished, 1980)	Norbach et al., 1980

* Animals were exposed to 5.4 or 1.5 mg/m³ of Aroclor 1254 for 7 hours/day, 5 days/week for 17 weeks. To approximate dose in mg/kg/day, the following corrections were applied: 0.2 (volume of air breathed in m^3 by animal per day); 0.5 (weight of animal in kg); 24/7 (correction for 24 hour/day exposure); 7/5 (correction for 7 day/week exposure). Resulting value assumes 100% absorption.

** Total dose in gm/kg

TABLE II - OCCUPATIONAL EXPOSURE TO PCBs

Study	Exposure Level & Time	Study Population Exposed	Study Population Controls	Findings: Dermal Effects	Findings: Liver Function	Findings: Blood Concentrations	Findings: Cancer/ Mortality	Comments
Helge 1954: Outbreak of dermatitis in a chemical plant	0.1 mg/$_m$3 Aroclor® - 5 to 19 mos. intermittent exposure through vapor leakage	14 potentially exposed	0	7 mild to moderate chloracne, contact dermatitis	6 normal, 1 borderline abnormal			There was not a good correlation between apparent degree of exposure and development of signs of disease
Hasegawa et al., 1972: Study of 6 industrial plants including PCB manufacturing, capacitor, manufacture, and biphenyl recovery	Vapors: 13-965 ug/$_m$3 Particulates: 4-650 (6,270 in a spill) <1 to 20 years	99	32	Various	Slightly abnormal	Exposed: 370 ppm Nonexposed: 20 ppm		Dermal ailments were unrelated to blood centrations; based on 3 plants, there was no relationship of exposure to blood concentrations, fat metabolism was apparently affected.
Hara et al., 1973-1974: Study concentrated on 17 immersion process worker	Level of exposure not reported in NIOSH Criteria Document	118		45% blackheads, 37% acne, 13% irritation	not reported	Exposed: 7-300 ppb		Effects correlated with duration of exposure; one year later blood concentrations were decreased by varying amounts. The longer the duration of exposure, the longer the PCB half-life in blood.

TABLE II- OCCUPATIONAL EXPOSURE TO PCBs (cont'd)

Kitamura 1973: Study of workers in a capacitor manufacturing plant	Exposure level not reported in NIOSH Criteria Document; duration 2.5 yrs.	13		Various: acne, seborrhea, adiposa, etc.	Normal	Average: 820 ppb (range: 320 -2100 ppb)	No relationship was found between concentration in blood and duration of exposure.
Innue et al., 1975: Study of a family exposed during milk thread glossing operation.	Not reported in NIOSH Criteria Document	Family members and 1 helper. (Later 54 more persons were studied)		Skin lesions and comedones on face and back	Unknown	130-250 ppb	PCBs were found in mothers' milk
Sato and Hasegawa 1974: Pressure sensitive carbonless paper manufacturer	0.13 - 4.4 ug/m^3 and 0.15 - 1.2 (measured 2 yrs. past PCB use)	Not reported in NIOSH Criteria Document				Exposed: 73 ppb Nonexposed: 20 ppb	
Karppanen and Kolho 1972: Study of 3 groups: 1) no exposure 2) analytical lab workers 3) capacitor impregnation workers (Aroclor 1242)	Low, medium and high exposure < 1 mg/m^3 (with skin protection)	High exposure: 8 males 4 females Medium exposure: 6 females	4 males 5 females			Unexposed: 5.6 - 12 ppb Medium 36-63 ppb High exposure 74-1,900 ppb	No biologic effect observed.
Bumgarner et al., 1973: Study of refuse workers exposed to PCB in incineration of waste	Incinerated waste	37	36 lumber yard workers			Measurable concentrations in 32 of the 37 refuse workers (4-14 ppb)	Concentrations not well correlated with duration of exposure.

TABLE II- OCCUPATIONAL EXPOSURE TO PCBs (cont'd)

Ouw et al., 1976: Study of capacitor manufacturer workers.	Aroclor 1242: 1.1 - 1.4 mg/m3 (19 workers); 0.32 mg/m3 (15 workers) Workers wore no protective clothing. Time 1 mo. to 23 yrs.	34	30	Mild burning, irritation of face, eyes and skin; 5 had rashes 1 chloracne, several dermatitis	BSP elevated in 4 of 7 with blood levels > 500 ppb	Exposed: 100 - 602 ppb (mean 400 ppb). Not detected in nonexposed.		Systemic effects reported such as nausea and persistent body odor. There was no adverse response at blood concentrations below 200 ppb.
Bahn, et al., 1976: Study of workers in a refinery	Aroclor 1254 over a 9 yr. period	31 males and 41 females					2 malignant melanomas observed, .04 expected (based on TNCS data)	These were preliminary results reported in a letter to the editor. Workers were also exposed to other chemicals. Study is in progress.
Brown and Jones 1980: Cohort mortality study of capacitor manufacturers	Aroclor 1016 Plant 1: 24 - 393 ug/m3 Plant 2: 170 - 1260 ug/m3	Plant 1: 968 Plant 2: 1,599				All cause mortality was lower than expected (163 obs. vs. 174 exp.) All cancer mortality was lower than expected (39 obs. vs 40.6 exp.) Rectal and liver cancer were slightly elevated but not significantly.		Lower observed mortality attributable to the "health worker" effect. NIOSH will continue to follow-up mortality experience.

TABLE II- OCCUPATIONAL EXPOSURE TO PCBs (cont'd)

Baker, Landrigan et al., 1980: Study of exposure to PCBs in sewage sludge.	Liquid sewage entering plant 30-470 ppb. Upstream sewage 1250-5500 ppb (Aroclor 1016) Concentrations in sludges (Aroclor 1242) were as high as 1700 ppm (mean 479.1 ppb) and 107.3 ppm in treated soil (mean 17.1 ppm)	89 sludge users, 18 workers exposed to PCBs, 19 members workers families	22 community members	Acne, increased pigmentation in 4 workers		Sludge users 17.4 ppb; workers 75.1 ppb; families 33.6 ppb; community 24.2 ppb	Plasma triglyceride levels increased significantly with serum PCB concentrations. Data indicate that PCBs may alter lipid metabolism.
Fishbein, et al., 1979: Cross-sectional field survey of capacitor manufacturing workers.	None, low, medium, high based on job classification and air monitoring (high- 0.6-11 mg/m^3 TWA) duration 40% $\geq$ 20 yrs. 10% $<$ 5 yrs.	326 currently employed, 27 retirees (not broken down into exposure categories for most endpoints monitored).	None	Apparent increase in prevalence of various dermatologic complaints including 35 with history of acne since onset of employment and 16 with acneform rash on examination.	Statistical significance associated with SGOT with serum levels of PCB but low incidence of "abnormal" values; no association with other liver enzymes.		Results severely limited by fact that there was no attempt to correlate exposure or blood levels with endpoints being measured - so that no possibility of observing "dose-response" effect or even exposed vs control differences.

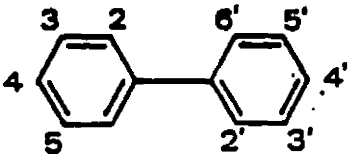
TABLE III

PERCENT DISTRIBUTION OF SYMPTOMS OF YUSHO REPORTED BY 189 PATIENTS EXAMINED BEFORE OCTOBER 31, 1968.

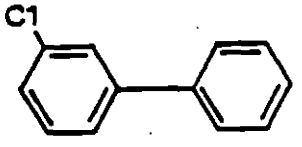
Symptoms	Males (N-89)	Females (N- 100)
Dark brown pigmentation of nails	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	75.3	72.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet and palms of hands	24.7	29.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness in limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasm of limbs	7.9	8.0
Headache	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

Source: Kuratsune et al, 1972

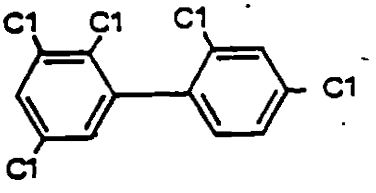
FIGURE I



BIPHENYL MOLECULE AND RING NUMBERING SYSTEM



3-chlorobiphenyl



2,2',3,4',5-pentachlorobiphenyl

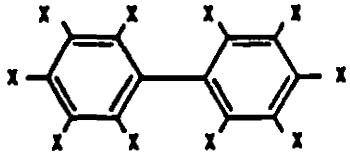
EXAMPLES OF NOMENCLATURE SYSTEM OF CHLOROBIPHENYL COMPOUNDS

NUMBER OF ISOMERS AND PERCENT CHLORINE FOR THE 10 CHLOROBIPHENYL (PCB) CLASSES

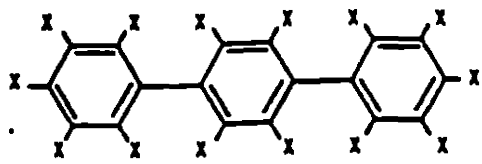
Chlorobiphenyl	Empirical Formula	No. of Isomers	Weight % Cl
mono	$C_{12}H_9Cl$	3	18.79
di	$C_{12}H_8Cl_2$	12	31.77
tri	$C_{12}H_7Cl_3$	24	41.30
tetra	$C_{12}H_6Cl_4$	42	48.56
penta	$C_{12}H_5Cl_5$	46	54.30
hexa	$C_{12}H_4Cl_6$	42	58.93
hepta	$C_{12}H_3Cl_7$	24	62.77
octa	$C_{12}H_2Cl_8$	12	65.98
nona	$C_{12}HCl_9$	3	68.73
deca	$C_{10}Cl_{10}$	1	71.18

Source: NIOSH, 1977

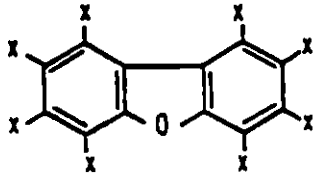
FIGURE II



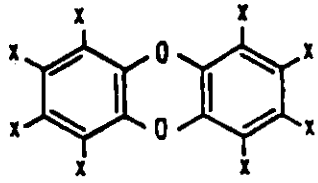
Polychlorinated Biphenyls (PCB's)



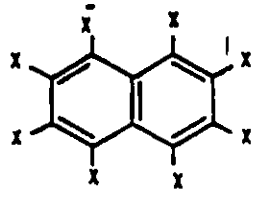
Polychlorinated Terphenyls



Chlorinated Dibenzofurans



Chlorinated Dibenzodioxin



Polychlorinated Naphthalenes

Source: Kimbrough, 1974

FIGURE III

CHLORODIBENZOFURAN TYPES AND CONCENTRATIONS (µg g) IN COMMERCIAL PCB PREPARATIONS

	Chlorodibenzofurans						
Mixture*	di	tri	tetra	penta	hexa	hepta	Total
(1) 1016	0.5						0.5
(1) 1016			<0.0001	<0.0001	<0.0001		
(1) 1248			0.5	1.2	0.3		2.0
(1) 1254			0.1	0.2	1.4		1.7
(1) 1254			0.2	0.4	0.9		1.5
(1) 1260			0.1	0.4	0.5		1.0
(1) 1260			0.2	0.3	0.3		0.8
(2) A-60			1.4	5.0	2.2		8.4
(3) DP-6			0.7	10.0	2.9		13.6
(4) K300			(a)	(a)			1-1.5
(4) K400	(c)***	(e)	(e)	(c)			17-18
(4) K500				(a)	(c)	(a)	2,5-4
(4) K600			(a)	(a)	(b)	(b)	3-5

*(1) Aroclor, (2) Clophen, (3) Phenoclor, (4) Kanechlor
**(a), (b), (c), (d), (e) represent relative amounts in increasing order

783594

Source NIOSH, 1977

FIGURE IV

Responses of primates and rats to PCB's*

Response	Man	Monkey	Rat
Susceptibility to toxicity	High	High	Moderate
Acne	Yes	Yes	No
Hyperpigmentation of skin	Yes	Only infants	No
Alopecia	NA	Yes	No
Hyperactive Meibomian glands	Yes	Yes	No
Conjunctivitis	Yes	Yes	No
Oedema of eyelids	Yes	Yes	No
Subcutaneous oedema	Yes	Yes	No
Keratin cysts in hair follicles	Yes	Yes	No
Hyperplasia of hair follicle epithelium	Yes	Yes	No
Gastric hyperplasia	NA	Yes	No
Thymic atrophy	NA	NA	Yes
Hepatic hypertrophy	Yes	Yes	Yes
Liver enzyme change	NA	Yes	Yes
Decreased no. of red-blood cells	Yes	Yes	No
Decreased haemoglobin	Yes	Yes	No
Serum hyperlipidaemia	Yes	Hypolipidaemia	Yes
Leucocytosis	Yes	Yes	No

Source: IARC, 1978

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* This table summarizes acute and subacute clinical effects but does not include chronic or delayed effects such as reproductive effects or cancer.