

# TENACIOUS TOXINS OF INDUSTRIAL ORIGIN: POLYCHLORINATED BIPHENYLS (PCBs)

BY

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## ILLUSTRATIVE FACTUAL PROBLEMS

### *North Carolina:*

Dirt contaminated by PCB illegally sprayed along state roadways four years ago was trucked and dumped at a landfill in Warren County.

### *Minnesota, Iowa and Wisconsin:*

Produce from 700 grocery stores was recalled by a food wholesale firm because of a leak of PCBs at a warehouse in Hopkins, Minnesota. The leak from an electrical transformer may have contaminated sweet corn, raisins, and prunes.

### *Montana:*

High levels of PCBs, 17 times higher than the amount allowed in domestic poultry, were found in ducks and predator birds. It is not known how the PCBs entered the food chain. Hunters were warned not to eat wild game birds without trimming all fat and discarding internal organs, skin and drippings; and to cook the bird thoroughly without stuffing. Pregnant and lactating women were advised not to eat the game birds.

### *Michigan:*

Grain silos built or repaired between 1941-1966 used a PCB-containing sealant to prevent corrosion

of the silos' linings. A survey begun in May 1981 showed PCBs in 253 of 8569 silos built by one company who also built silos in Ohio.

### *California:*

Leaking of PCB, an oily flame retardant widely used in capacitors, transformers and other electrical equipment, has become a nation-wide health danger, according to EPA in 1981. The California legislature held hearings on a bill requiring marking of utility poles holding electrical equipment containing PCBs. Firemen testified that the location of these utility lines is often unknown, and that they are endangered by leaking PCBs in power line fires. In August 1981, firefighters noted traces of PCB escaped with a gas line rupture in San Francisco. The utility company said it is their policy to notify firemen and people in the area of PCB leakage.

Cleanup of highly toxic PCB from a rupture electrical capacitor required a crew of 8 men to remove fences, shrubs and boxes of earth from three backyards in Orange County. Tests inside three homes in the area were done by wiping samples on gauze; these samples were sent to a laboratory for analysis of contamination by PCBs.

A capacitor attached to a utility pole caught fire

## TRAUMA

at 4 p.m., spilling two gallons of fluid containing PCBs. The spill did not touch any people, but several vehicles and the sidewalk area around the pole were sprayed. Utility company crews cleaned up the spill and continued to monitor the area the following morning.

### *Chicago, Long Island and Southern California:*

Liquid PCB has been found in natural gas systems in these three areas. Southern California Gas Co. found liquid PCB as high as 200 parts per million in some samples; San Diego Gas and Light Co. tests showed a sample with 1000 parts per million. A Long Island gas firm found PCBs when testing an oily resi-

due in a gas meter. EPA's "guess" is that entry of PCBs into the gas systems occurred from a lubricant for pipelines or compressors, possibly many years ago. As of March 1981, EPA did not have methodology for testing natural gas for PCB, and testing for airborne PCBs in homes and businesses would be difficult.

### *New York:*

An 18-story building in Binghamton was contaminated inside and out by PCB-containing ash after an electrical transformer burst during a fire in the basement. The building was evacuated, and clean-up begun.



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Dr. Johnsen's major research interest is the nature, distribution and persistence of pesticide residues in plants, animals and the environment; and he has published over 22 articles in his field of interest. He is certified and licensed to use radio-labelled materials in metabolic studies, and has extensive experience with gas-liquid, thin-layer and column chromatography, infra-red and ultraviolet spectrophotometry, and wet-chemical techniques in sample analysis. His professional memberships include the American Chemical Society, ACS Division of Pesticide Chemistry, Entomological Society of America, American Association for the Advancement of Science, American Society for Microbiology, Society of Sigma Xi, Gamma Sigma Delta, and the New York Academy of Science. Dr. Johnsen has also been a consultant on toxicology to the City of Fort Collins on PCB pollution, the Colorado Department of Agriculture on special need registration of pesticides in the state, and to attorneys on insecticide toxicology.



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## INTRODUCTION

The natural world today contains a vast assortment of man-made chemicals, many of which have no known counterpart to the equally vast array of biologically derived chemicals.

Because of their uniqueness, biological systems have not been able to metabolize or degrade them readily as they do biological chemicals, with the resultant effect that they can accumulate in various components of the ecosystem. This is evident for the well-known insecticide DDT and its major persistent metabolite DDE.

Pollution of the global environment by the activities of mankind is justifiably receiving greatly increased attention. The serious ecological concerns brought on by the large-scale use of agricultural pesticides, especially those of the chlorinated hydrocarbon insecticides such as DDT, endrin or dieldrin, or herbicides such as 2,4,5-T, have made the general public keenly aware of environmental contamination and potential or real health effects. These concerns have culminated in the banning of both DDT and 2,4,5-T and very restrictive use patterns for dieldrin and endrin in recent years.

Since the late 1960s, public and governmental eyes were focused on still another chlorinated hydrocarbon, the polychlorinated biphenyls, commonly referred to as PCBs. The PCBs are industrial chemicals of great utility which had been produced since 1929, and it wasn't until 1966 that evidence of their widespread environmental incidence became known. They were not even suspected of being potential pollutants because they were never distributed deliberately into the environment as were pesticides, and their use patterns differed markedly.

## SCOPE OF PROBLEM

Mr. Russell Train, EPA Administrator in 1976, presented a statement before a congressional sub-committee on January 28, where he outlined the problem with PCBs (Train, 1976).

### PERSISTENT SOURCES

He estimated that over the past 45 years (through 1975), some 1.4 billion pounds (700,000 tons) of PCBs were produced in the U.S., and over half of this amount had already entered the environment through discharges to the air, water and land. He stated further that, although some had been degraded, the vast majority is contained in:

- 1) Landfills.
- 2) Soils.
- 3) Sediments of rivers, lakes and coastal waters.

### USES

Mr. Train reported that over 700 million pounds were currently in use in:

- 1) Electrical equipment such as transformers and capacitors.
- 2) Hydraulic equipment.
- 3) Paper products.
- 4) Other commercial and industrial products.

Without preventive measures, he stated that essentially all of these PCBs could ultimately enter the environment. His talk was a prelude to the passage of the Toxic Substances Control Act, passed by Congress later in 1976.

## POLYCHLORINATED BIPHENYLS (PCBs)

### YUSHO DISEASE: OVER 1000 CASES OF PCB POISONING

The human health significance of the PCBs came to public attention in 1968 when over 1000 Japanese became ill after eating rice oil contaminated with PCBs from an undetected leak in heat-transfer equipment used to heat the rice oil; the illness was called "Yusho" or rice oil disease.

#### SYMPTOMS

The exposed people subsequently developed:

- 1) Chloracne.
- 2) Headache.
- 3) Nausea.
- 4) Vomiting.
- 5) Peripheral numbness.
- 6) Menstrual irregularity.
- 7) Gastrointestinal disturbances.
- 8) Many other non-specific signs and symptoms (Kuratsune et al., 1972).

### PCBs DETECTED IN HUMAN AND ANIMAL TISSUES

Since 1966, PCBs have been detected in human foods and tissues, including milk, many forms of wildlife, especially fish, and numerous other components of the environment in the U.S. and other industrialized parts of the world (WHO, 1976).

#### LONGTERM CONSEQUENCES UNKNOWN

The longterm consequences of PCBs to humans generally are unknown, although information indicates they may be carcinogenic to laboratory rodents (Kimbrough and Linder, 1974; Kimbrough et al., 1975).

Domestic production of PCBs was stopped in October 1977 by the sole U.S. manufacturer (Hatton, 1979).

### DEVELOPMENT

The PCBs were known as early as 1881 (Schmidt and Schultz, 1881), but large scale production did not begin until 1929 when commercial quantities of inexpensive biphenyl became available (Jenkins et al., 1930) and the physical characteristics and commercial possibilities were publicized (Penning, 1930).

#### SYNONYMS

The following are all synonyms for the PCBs:

- 1) Chlorinated biphenyl.
- 2) Chlorinated diphenyl.
- 3) Chlorobiphenyl.
- 4) PCB.
- 5) Polychlorinated biphenyl.
- 6) Polychlorobiphenyl (IARC, 1978).

#### COMMERCIAL PREPARATION

PCBs are prepared commercially by reacting biphenyl with anhydrous chlorine at elevated temperatures using a catalyst such as ferric chloride or iron turnings. The products are complex mixtures of chlorinated biphenyls whose degree of chlorination depends upon the contact time of the biphenyl with chlorine. After washing, the chlorinated products are batch-distilled to remove color and traces of hydrogen chloride (EPA, 1976). Details of manufacture can be found in Hubbard (1964).

#### INDUSTRIAL USES

Commercial development expanded in response to the electrical industry's need for an improved dielectric fluid (non-conduct of direct current) for use in transformers and capacitors to provide fire resistant qualities and to replace the mineral



oil formerly used in these applications (Hatton, 1979).

Their fire resistant nature made them excellent choices as hydraulic and heat transfer fluids; and PCBs were found to increase the waterproofing characteristics of surface coatings and to be advantageous to manufacturers of carbonless copy paper, printing inks, plasticizers, paints, adhesives, lubricants, vacuum pump fluids and many other applications (Hatton, 1979; Hubbard, 1964).

## CHEMICAL COMPOSITION

### MANY COMPONENTS WITH VARYING CHLORINE CONTENT

Commercial PCB products are mixtures of many components with varying chlorine content. The properties of these components, and hence the products, are vastly different and very complex to study.

### AROCLOR

Although PCBs have been produced in about eight countries, the sole U.S. producer, until cessation of production, was the Monsanto Co. which marketed as many as 13 products under the trade name Aroclor.

The PCBs in the Aroclor series are identified by a four-digit numbering code. The first two digits, 12, indicate the parent material is biphenyl, and the last two digits the weight percent of chlorine. For example, Aroclor 1248 is a chlorinated biphenyl containing 48% chlorine. Aroclor 1016 is an exception. It is of more recent vintage being a distillation product of Aroclor 1242 containing less than 1% of components with five or more chlorine atoms (WHO, 1976) even though it contains 41% chlorine (Mieure et al., 1976). Each Aroclor mar-

keted is a complex mixture varying from 6 components in 1221 to more than 70 for 1254 (Sissons and Welti, 1971). Terphenyls (3 phenyl groups) are indicated by a 54 in the first two digits and blends of biphenyls and terphenyls by either a 25 or 44 (75% and 60% PCBs, respectively) (Hutzinger et al., 1974).

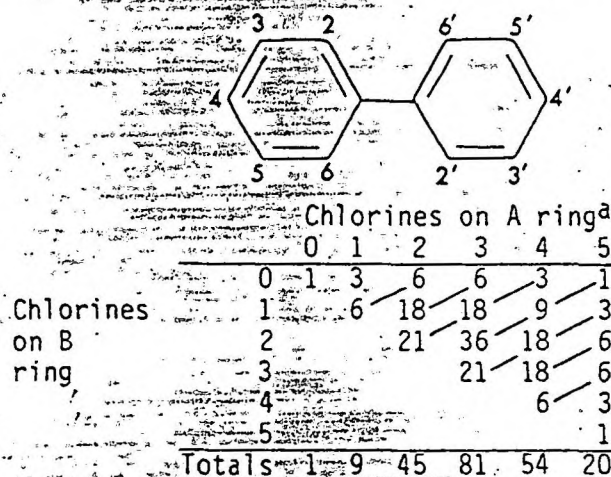
Figure 1 illustrates that with biphenyl as the parent material, there are 209 theoretically possible chlorinated products from the 10 positions on the biphenyl molecule (as numbered) available for chlorine substitution.

From Figure 1, one can conclude that there can be 3 different monochloro derivatives, 12 different dichloro, 42 tetrachlorobiphenyls, etc. However, it is highly unlikely that all of them will be formed. Most likely absent would be a PCB fully chlorinated on one ring and not at all on the other (e.g. 2,3,4,5,6-pentachlorobiphenyl) (Hutzinger et al., 1974). A good description of the system of nomenclature for the various PCB derivatives can be found in Hutzinger et al. (1974).

### IDENTIFYING INDIVIDUAL PCBs

There have been several studies to identify individual PCBs in commercial preparations. Sissons and Welti (1971) separated the components of Aroclor 1242, 1254 and 1260 using both column and gas-liquid chromatography (GLC) and characterized many of the peaks by mass spectrometry (MS) and high resolution nuclear magnetic resonance spectroscopy (NMR). They found in excess of 70 peaks by GLC for Aroclor 1254 which included identification of 16 major components and characterization of 56 minor constituents. They also identified the structure of 45 components in 1242 and 78 in Aroclor 1260. Many of

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<sup>a</sup> modified from Cook (1972)

FIG. 1. The Numbering System for the Biphenyl Structure and the Theoretical Numbers of Combinations Possible of Chlorines in the Two Rings of Biphenyl.

Table 1  
TYPICAL PERCENTAGE OF COMPOSITION OF SOME AROCLORS

| No. of Cl/<br>biphenyl | AROCLOR           |                   |                   |                   |                   |                   |
|------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                        | 1221 <sup>a</sup> | 1242 <sup>a</sup> | 1016 <sup>a</sup> | 1248 <sup>b</sup> | 1254 <sup>a</sup> | 1260 <sup>b</sup> |
| 0                      | 11                | 0.1               | 0.1               | —                 | 0.1               | —                 |
| 1                      | 51                | 1                 | 1                 | —                 | 0.1               | —                 |
| 2                      | 32                | 16                | 20                | 2                 | 0.5               | —                 |
| 3                      | 4                 | 49                | 57                | 18                | 1                 | —                 |
| 4                      | 2                 | 25                | 21                | 40                | 21                | 1                 |
| 5                      | 0.5               | 8                 | 1                 | 36                | 48                | 12                |
| 6                      | N.D. <sup>c</sup> | 1                 | 0.1               | 4                 | 23                | 38                |
| 7                      | N.D.              | 0.1               | N.D.              | —                 | 6                 | 41                |
| 8                      | N.D.              | N.D.              | N.D.              | —                 | N.D.              | 8                 |
| 9                      | —                 | —                 | —                 | —                 | —                 | 1                 |

<sup>a</sup> Mieure et al. (1976).

<sup>b</sup> Hammond et al. (1972)

<sup>c</sup> None detected (<0.01%)

these components in 1254 were found also in 1242 and 1260, with the former containing lower chlorinated derivatives and the latter more highly chlorinated products. They found the predominant species in

1254 to be pentachlorobiphenyls, in 1242 to be tri- and tetrachloro derivatives and in 1260 to be hexa- and heptachlorobiphenyls. Table 1 summarizes the typical composition of several Aroclors.

# VARIATIONS IN COMPOSITION FROM BATCH TO BATCH

Table 2  
PCB IDENTIFYING CHEMICAL DATA  
AND TOXICITY<sup>a</sup>

It should be acknowledged that commercial PCBs are not sold on a composition basis but rather on their physical properties so there can be variations in composition from batch to batch of the same Aroclor or other tradename.

Sissons and Welti (1971) noted that 2,4,6-substitutions rarely occur and 3-, 3,5- and 2,3-substitutions occur infrequently. Webb and McCall (1972) identified the GLC peaks in Aroclors 1221-1254 with those of synthesized compounds by retention times and infrared spectrometry (IR). Jensen and Sunstrom (1974), in the most extensive study, were able to characterize and quantify 60 components of Clophens A-50 and A-60 from Germany which indicated the close similarity of components of Aroclor 1254 and Clophen A-50.

The listing of PCBs marketed in the U.S. by Monsanto along with identifying Chemical Abstracts Registry Number and acute toxicity are presented in Table 2.

| Name                                   | CAS <sup>b</sup> | LD <sub>50</sub> <sup>c</sup> |
|----------------------------------------|------------------|-------------------------------|
| Biphenyl                               | 92-42-4          | 3280                          |
| Polychlorinated biphenyls <sup>d</sup> | 1336-36-3        | —                             |
| Aroclor 1221                           | 11104-28-2       | 3950                          |
| Aroclor 1232*                          | 11141-16-5       | 4470                          |
| Aroclor 1242                           | 53469-21-9       | 4250                          |
| Aroclor 1248*                          | 12672-29-6       | 11000                         |
| Aroclor 1016                           | —                | —                             |
| Aroclor 1254                           | 27323-18-8       | 1295                          |
| Aroclor 1260*                          | 11096-82-5       | 1315                          |
| Aroclor 1262*                          | 37324-23-5       | 11300                         |
| Aroclor 1268*                          | 11100-14-4       | 10900                         |
| Aroclor 2565                           | 37324-24-6       | 6310                          |
| Aroclor 4465                           | 11120-29-9       | 16000                         |
| Aroclor 5442                           | 12642-23-8       | 10600                         |
| Aroclor 5460                           | 11126-42-4       | 19200                         |

<sup>a</sup> Data from NIOSH, 1979

<sup>b</sup> Chemical Abstracts Registry Number

<sup>c</sup> Oral lethal dose fatal to 50% of exposed rats; mg/kg of body weight

<sup>d</sup> A listing of CAS numbers for 38 individual chlorinated PCBs can be found in IARC (1978)

\* Discontinued manufacture prior to 1976 (Mieure et al, 1976)

## NO HIGH ACUTE TOXICITY; EFFECTS FROM PROLONGED, CHRONIC EXPOSURE

It should be noted that none of the PCBs listed have high acute toxicity. As will be shown, the deleterious effects arise primarily from prolonged chronic exposure.

In Germany, products marketed as Clophen A50 and A60 contained 54 and 64% chlorine, respectively; in France, Phenoclor DP6 contained 60% chlorine; and in Japan, Kanechlor 300, 400, 500, and 600 contained approximately 42, 48, 54, and 60% chlorine, respectively (NIOSH, 1977). These products are very similar to their Aroclor counterparts in composition.

## PRODUCTION

Produced commercially since 1929 in the U.S., it has been estimated that some 495,000 tons of PCBs had been sold in North America by 1970 (Interdepartmental Task Force on PCBs, 1972). Another reference reported domestic sales of 795 million lbs (398,000 tons) of PCBs for the years 1957 through 1974 (Kleinert, 1976). If these figures are both correct, then domestic sales were expanding markedly, especially in the 1960s. Table 3 lists domestic production by Monsanto from 1960 to 1971 (Anonymous, 1971) and indicates this growth.



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Table 3

## DOMESTIC PRODUCTION OF PCBs BY MONSANTO CO. IN SHORT TONS

| Year   | DOMESTIC SALES      |                                 |                     |         |
|--------|---------------------|---------------------------------|---------------------|---------|
|        | U.S. Production     | Insulating Liquids <sup>a</sup> | Others <sup>b</sup> | Exports |
| 1960   | 20,786              | 12,444                          | 5,163               | 1,827   |
| 1961   | 20,333              | 11,108                          | 7,661               | 2,076   |
| 1962   | 20,986              | 11,683                          | 7,339               | 1,809   |
| 1963   | 22,367              | 11,448                          | 7,618               | 1,824   |
| 1964   | 25,417              | 13,969                          | 8,666               | 2,048   |
| 1965   | 30,240              | 16,203                          | 9,695               | 2,117   |
| 1966   | 32,925              | 18,897                          | 10,642              | 3,426   |
| 1967   | 37,655              | 20,387                          | 10,846              | 4,062   |
| 1968   | 41,427              | 20,568                          | 11,990              | 5,616   |
| 1969   | 38,194              | 18,564                          | 15,034              | 5,312   |
| 1970   | 42,527              | 20,268                          | 16,263              | 6,826   |
| 1971   | 20,236 <sup>c</sup> | 14,417                          | 4,401               | 4,938   |
| Totals | 353,093             | 189,756                         | 115,318             | 41,881  |

<sup>a</sup> For closed electrical systems-transformers and capacitors

<sup>b</sup> Includes heat-transfer systems, hydraulics/lubricants, and plasticisers

<sup>c</sup> Estimated

### VOLUNTARY RESTRICTION OF PRODUCTION

Table 3 indicates that 1971 production was less than half its 1970 production and that PCB sales for uses other than electrical insulation had dropped more than 70% to 4,401 tons. This latter point was doubtless due to Monsanto in mid-1970 voluntarily restricting sales of PCBs for uses where end-product disposal could not be controlled due to the overwhelming accumulation of evidence of its environmental contamination.

### OVER 350,000 TONS IN ENVIRONMENT

Train (1976), cited earlier, had estimated total U.S. production from 1929 through

1975 to be about 700,000 tons with over half of this, 350,000+ tons, already in the environment. Data for production estimates of individual Aroclors are scarce and should indicate relative volumes of different Aroclors. Available data is presented in Table 4 and does not include exports or total production figures.

Table 4 indicates that there was a wide variation in production, with Aroclor 1242 having over three times the tonnage of the runner-up Aroclor 1254. It is interesting to note that in only four years, there were over 34,000 tons of Aroclor 1016 sold. Aside from 1016, the production of PCBs of 42-60% chlorine accounted for almost 88% of the total sales of Aroclors during this period.

Table 4

DOMESTIC SALES OF  
DIFFERENT AROCLORS FROM  
1957 THROUGH 1974

| Aroclor           | Tons    |
|-------------------|---------|
| 1221              | 2,761   |
| 1232 <sup>a</sup> | 1,019   |
| 1242              | 215,608 |
| 1248 <sup>b</sup> | 29,603  |
| 1254              | 61,861  |
| 1260 <sup>b</sup> | 45,774  |
| 1262 <sup>a</sup> | 7,175   |
| 1268 <sup>c</sup> | 1,441   |
| 1016 <sup>d</sup> | 34,861  |
| Total             | 401,103 |

Reference: Bremer (1975)

<sup>a,b,c</sup> Zero sales starting in 1972;1973<sup>b</sup>; 1971<sup>c</sup><sup>d</sup> Sales began in 1971

## FOREIGN PRODUCTION

Data for PCB production and sales by other countries is quite limited. Japan first produced PCBs in 1954, the Kanechlor series, and by 1972 had produced 58,787 tons with over 11,000 tons in 1970 alone, but suspended all production in 1972 (Tatsukawa, 1976). In 1973, production, exportation and importation in a number of countries were reported as shown in *Table 5*.

## USES

The PCBs are a class of aromatic, chemically inert, chlorinated hydrocarbons which have had very broad applications until being severely restricted in 1971. Although manufacture of PCBs ceased in October 1977, residues of PCBs from prior and current uses are still appearing in environmental media.

*Table 6* lists the manufacturers of products containing PCBs as of 1979 (EPA, 1979). As is indicated, there are many industrial concerns involved in utilizing PCBs, although Monsanto was the sole producer with plants in Anniston, Alabama, where PCB production ended in 1970, and Sauget, Illinois, where production ceased in 1977 (NAS, 1979).

## CAPACITORS AND TRANSFORMERS

Most of those listed in *Table 6* are involved in manufacturing sealed-use products such as capacitors and transformers.

## FOREIGN PCB USAGE

Data for PCB usage in other countries is either absent or few in number. IARC (1978) reported uses of PCBs in 1973 for the U.S. (19,000 tons), France (5936 tons), Italy (2932 tons), Canada (1422 tons), UK (1268 tons) and Belgium (783 tons) with considerably smaller amounts for several other OECD members. Bergland (1972) reported that Sweden in 1970 imported about 500 tons with about 50% of this exported to other countries in electric capacitors and that, in 1968, 65 tons were used in dyes which was reduced to 35 tons in 1970.

## 1,000,000 TONS PRODUCED SINCE 1929

With Train (1976) estimating that U.S. total production through 1975 was some 700,000 tons, it can be surmised that total world production since 1929 could approximate 1,000,000 tons. Such an estimate underscores the concern produced worldwide and the continuing efforts to understand the potential toxicological implications.

(Text continued on page 2:57)



# POLYCHLORINATED BIPHENYLS (PCBs)

Table 5

## PRODUCTION, EXPORTATION AND IMPORTATION OF PCBs BY COUNTRY IN 1973

| Country                    | Production <sup>a</sup><br>(tons) | Exportation<br>(tons) | Importation<br>(tons) |
|----------------------------|-----------------------------------|-----------------------|-----------------------|
| United States <sup>b</sup> | 20,233                            | 2,698                 | 258                   |
| France                     | 10,692                            | 5,071                 | 331                   |
| United Kingdom             | 4,519                             | 4,189                 | 5                     |
| Italy                      | 2,756                             | 1,213                 | 1,764                 |
| Canada                     | —                                 | —                     | 1,213                 |
| Finland                    | —                                 | —                     | 266                   |
| New Zealand                | —                                 | —                     | 20                    |
| Norway                     | —                                 | —                     | 20                    |
| Sweden                     | —                                 | —                     | 350                   |

<sup>a</sup> Austria, Czechoslovakia, West Germany (FRG), Spain and the USSR produced PCBs in 1973 but quantities unknown.

<sup>b</sup> U.S. data for 1974.

References: Hutzinger (1974); EPA (1976); IARC (1978); Durfee (1976).

Table 6

## MANUFACTURERS AND TRADE NAMES OF PCBs BY COUNTRY

Many manufacturers have used PCBs in their products and/or marketed them under various trade names. This list may not be complete or current.

A. United States: C or T indicates manufacturer of capacitors or transformers.

| Manufacturer                  | Trade Name           |
|-------------------------------|----------------------|
| Aerovox (C)                   | Hyvol                |
| Allis-Chalmers                | Chlorextol           |
| American Corp.                | Asbestol             |
| Axel Electronics (C)          | —                    |
| Capacitor Specialists (C)     | —                    |
| Cornell Dubilier (C)          | Dykanol              |
| Dings Co.                     | —                    |
| Electric Utilities Corp. (C)  | Eucarel              |
| Electro Engineering Works (T) | —                    |
| Electromagnetic Filter Co.    | —                    |
| Envirotech Buell              | —                    |
| Eriez Magnets                 | Pyranol              |
| ESCO Manufacturing Co. (T)    | Askarel <sup>1</sup> |
| Ferranti-Packard Ltd.         | Askarel <sup>1</sup> |
| General Electric (C,T)        | Pyranol              |
| Geneva Industries             | —                    |



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Table 6 (continued)

| Manufacturer                   |                          | Trade Name                          |
|--------------------------------|--------------------------|-------------------------------------|
| H. K. Porter (T)               |                          | —                                   |
| Helena Corp. (T)               |                          | —                                   |
| HEVI-Duty Electric (T)         |                          | —                                   |
| I.T.E. Circuit Breaker         |                          | Non-Flammable Liquid                |
| Jard Corp. (C)                 |                          | Clorphen                            |
| Kuhlman Electric Co. (T)       |                          | Saf-T-Kuhl                          |
| McGraw-Edison (C)              |                          | Elemex                              |
| Maloney Electric               |                          | —                                   |
| Monsanto                       |                          | Aroclor, Therminol <sup>2</sup>     |
| Niagara Transformer Corp. (T)  |                          | Pydraul <sup>3</sup> , Santovac 1&2 |
| P. R. Mallory & Co. (C)        |                          | Askarel <sup>1</sup> , EEC-18       |
| Power Zone transformer         |                          | Aroclor B                           |
| R. E. Uptegraff Mfg. (T)       |                          | EEC-18                              |
| R. F. Interonics (C)           |                          | —                                   |
| Reliance Electric Co.          |                          | —                                   |
| Research Cottrell (T)          |                          | Askarel <sup>1</sup>                |
| Sangamo Electric (C)           |                          | Diaclor                             |
| Sprague Electric Co. (C)       |                          | Chlorinol                           |
| Standard Transformer Corp. (T) |                          | —                                   |
| Stens Magnetics                |                          | —                                   |
| Tobe Deutschmann Labs (C)      |                          | —                                   |
| Universal Manuf. Co. (C)       |                          | Askarel <sup>1</sup>                |
| Van Tran Electric (T)          |                          | —                                   |
| Wagner Electric                |                          | No-Flamol                           |
| Westinghouse Electric (C,T)    |                          | Inerteen                            |
| York Electronics (C)           |                          | —                                   |
| B. Other Countries             |                          |                                     |
| Country                        | Manufacturer             | Trade Name                          |
| Czechoslovakia                 | Chemko                   | —                                   |
| France                         | Prodelec                 | Phenoclor, Pyralene <sup>4</sup>    |
| Germany (FRG)                  | Farbenfabriken Bayer     | Clophen                             |
| Italy                          | Caffaro                  | Dk, Fenclor, Inclor                 |
| Japan                          | Kanegafuchi Chemical Co. | Kanechlor                           |
| Japan                          | Mitsubishi-Monsanto      | Santotherm FR                       |
| United Kingdom                 | Monsanto                 | Aroclor, Pyroclor, Santotherm FR    |
| USSR                           | Sovol                    | —                                   |

<sup>1</sup> Askarel is the generic name for non-flammable insulating fluids in capacitors and transformers.

<sup>2</sup> Therminol included various products used as heat transfer fluids (e.g. Therminol FR-O)

<sup>3</sup> Pydraul included various products used as hydraulic fluids (e.g. Pydraul A-200).

<sup>4</sup> These products as now formulated, no longer contain PCBs.

References: EPA (1979), Hatton (1979), Durfee (1976).

# POLYCHLORINATED BIPHENYLS (PCBs)

Table 7

## USES OF PCBs IN THE U.S. BY AROCLOR TYPE SINCE 1970

| End Use                       | 1016 | 1221 | 1232 | 1242           | 1248 | 1254           | 1260           | 1262 | 1268 |
|-------------------------------|------|------|------|----------------|------|----------------|----------------|------|------|
| <b>Current Users:</b>         |      |      |      |                |      |                |                |      |      |
| Capacitors                    | X    | X    |      | X <sup>a</sup> |      | X <sup>a</sup> |                |      |      |
| Transformers                  |      |      |      | X              |      | X              | X <sup>a</sup> |      |      |
| <b>Former Uses:</b>           |      |      |      |                |      |                |                |      |      |
| Heat transfer                 |      |      |      | X              |      |                |                |      |      |
| Hydraulic/Lubricants          |      |      |      |                |      |                |                |      |      |
| Hydraulic Fluids              |      |      | X    | X              | X    | X              | X              |      |      |
| Vacuum pumps                  |      |      |      |                | X    | X              |                |      |      |
| Gas-transmission turbines     |      | X    |      | X              |      |                |                |      |      |
| Plasticizers                  |      |      |      |                |      |                |                |      |      |
| Rubbers                       |      | X    | X    | X              | X    | X              | X              |      | X    |
| Synthetic resins              |      |      |      |                | X    | X              | X              | X    | X    |
| Carbonless paper              |      |      |      | X              |      |                |                |      |      |
| <b>Miscellaneous</b>          |      |      |      |                |      |                |                |      |      |
| Adhesives                     |      | X    | X    | X              | X    | X              |                |      |      |
| Wax extenders                 |      |      |      | X              |      | X              |                |      | X    |
| Deducting agents              |      |      |      |                |      | X              | X              |      |      |
| Inks                          |      |      |      |                |      | X              |                |      |      |
| Cutting oils                  |      |      |      |                |      | X              |                |      |      |
| Pesticide extenders           |      |      |      |                |      | X              |                |      |      |
| Sealants & caulking compounds |      |      |      |                |      | X              |                |      |      |

\* Discontinued use  
Reference: EPA (1976)

### CURRENT AND FORMER USES

Principal current and former end uses of PCBs in the U.S. are presented in Table 7.

There have been many other applications not listed or not apparent from this table, such as:

- 1) Flame-proofing cellulose fabrics.
- 2) Constituents in elastomers, paints, lacquers, pigments and dyes.
- 3) Protective coatings for wood, metal and concrete.

4) Corrosion inhibitors (Hubbard, 1964).

All these uses ended ostensibly in 1971 with Monsanto's restricted sale of PCBs only for sealed systems.

### PRESENT USES

Principal uses today for PCB fluids are in the electrical industry and, with their superior cooling, insulating and dielectric properties, are used widely in capacitors and transformers. PCBs also give electri-



cal equipment the critical advantages of reliability, long life and compactness. PCB impregnated capacitors, for example, are markedly more reliable and long-lived, are one-sixth the size, one-fifth the weight and one-fourth the cost of comparable oil impregnated capacitors (Anonymous, 1972).

#### LIFE-EXPECTANCY OF PCB-CONTAINING TRANSFORMERS AND CAPACITORS

According to Durfee (1976), transformers containing PCBs comprise only about 5% of the U.S. transformer market and are used only where safety and reliability are of prime importance. Life expectancy of such PCB containing transformers was reported to be over 30 years, and some 135,000 have been put into service since 1932 with virtually all (as of 1973) still in service. The average transformer contains about 3,000 lbs of Askarel fluids of which 2,154 lbs are PCBs (NAS, 1979) which can give one an estimate of total use in this application alone.

Durfee (1976) reported data from General Electric which indicated that about 1 million capacitors containing PCBs are made in the U.S. annually, most for first-time use in products, and their life expectancy is over 10 years for lighting applications and over 20 years in electric utility service. The NAS (1979) report listed a high-voltage capacitor as weighing 120 lbs and containing 24 lbs of PCBs, while a low-voltage capacitor weighs about 20 lbs and contains 3.5 lbs of PCBs.

#### PROPERTIES

What properties do the PCBs have that have led to such widespread application over the years?

#### MIXTURES OF PCBs DIFFERENT FROM INDIVIDUAL COMPONENTS

Individual PCBs are of little commercial value whereas the mixed chlorinated components have considerable commercial significance. Mixtures of PCBs, as in the commercial Aroclors, have physical properties which are quite different from those of the individual components as can be seen in data of Hubbard (1964) and Hutzinger et al. (1974).

When isolated in pure form by recrystallization from suitable solvents, individual PCBs are usually white or colorless crystals; but commercial products usually are liquids because the melting point is depressed when components are mixed together (IARC, 1978).

#### INSULATION AND NON-FLAMMABILITY

The widespread adoption of PCBs by the electrical industry was due mainly to their excellent dielectric (insulating) properties and non-flammability. As their chemical and physical properties became known, uses for PCBs multiplied. Table 8 is a brief summary of their chemical and physical properties.

#### ACCUMULATION OF PCBs IN FATTY TISSUES

The solubility of PCBs in water is very low and decreases with increasing chlorine content; PCBs, therefore, accumulate in living matter, particularly in tissues and organs rich in lipids (Hutzinger et al., 1974).

A listing of the chemical and physical properties of representative Aroclors can be found in Hammond et al. (1972).



## POLYCHLORINATED BIPHENYLS (PCBs)

Table 8

### CHEMICAL AND PHYSICAL PROPERTIES OF PCB MIXTURES

1. Very high boiling point (very low vapor pressure)
2. Very low water solubility (high lipid solubility)
3. High dielectric constant (non-conducting)
4. High thermal stability (to 1600°F)
5. High resistance to acids, alkalies and corrosive chemicals.
6. High resistance to oxidation and environmental deterioration.
7. Permanently thermoplastic.
8. Vary from oily liquids to hard transparent resins.

Reference: Hubbard (1964)

## TOXIC IMPURITIES

Confounding the determinations of relative toxicities and potential and real environmental effects of PCBs are the findings that similar PCBs from different manufacturers show marked differences in toxicities to test animals.

Vos and Koeman (1970) and Vos and Beems (1971) found that Phenoclor DP-6 and Clophen A-60 were much more toxic to chicks and rabbits than Aroclor 1260, even though all three contain approximately the same degree of chlorination (60%).

## PCDFs AND PCNS

Subsequently, Vos et al. (1970) found that the Phenoclor and Clophen mixtures contained parts per million (ppm; ug/g) levels of:

- 1) Polychlorinated dibenzofurans (PCDFs), both tetra- and pentachloro forms.
- 2) Polychlorinated naphthalenes (PCNs), both hexa- and heptachloro forms.

## PCDFs AND TCDDs ("DIOXINS")

The PCDFs chemically are quite similar to the polychlorinated dibenzodioxins ("dioxins" or PCDDs) which gained worldwide notoriety during and subsequent to July 1976 when a chemical cloud was released from the ICMESA plant at Seveso, Italy. This cloud contained not only caustic 2,4,5-trichlorophenol but also 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Holmstedt, 1980). This form of TCDD is one of the most toxic chemicals known with an LD50 to male guinea pigs of 0.6 ug/kg and 22 ug/kg to male rats (Schwetz et al., 1973). Half a dozen books plus numerous publications resulted from this incident. TCDD is also discussed in many publications relating to the use of the herbicide 2,4,5-T in agriculture and the related Agent Orange as a defoliant in the Vietnam conflict (see Wilber, 1980).

Representative structures of a PCDD, PCDF and a PCN are given in *Figure 2*.

## BURNING OF PCB-CONTAINING FLUIDS: FORMATION OF "DIOXINS" AND PCDFs

It should be pointed out that dioxins in general, and TCDD in particular, have not

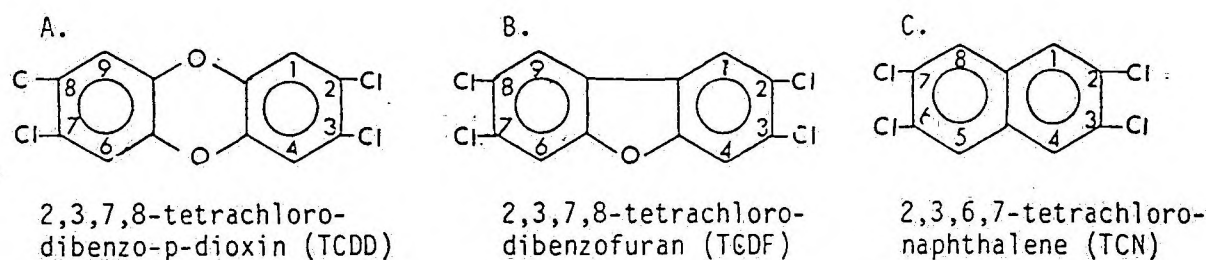


FIG. 2. Structures of a PCDD(A), PCDF(B) and a PCN(C)

been found in commercial PCBs, only PCDFs and PCNs. However, burning of PCB-containing transformer fluids such as Askarels, containing also chlorinated benzenes, has led to the formation of both PCDDs and PCDFs (Schechter et al., 1981); and pyrolysis of PCBs can lead to PCDFs (Buser et al., 1978a).

Buser and Rappe (1978) indicated that there are 75 positional compounds which could exist for the PCDDs containing from 1-8 chlorine atoms; and a number of these are known to be extremely hazardous compounds, especially the 2,3,7,8-TCDD. Buser et al. (1978b) reported that there are 135 positional isomers (isomerism—the possession by two or more distinct compounds of the same molecular formula, each molecule possessing an identical number of atoms of each element, but in different arrangement) possible for the PCDFs and some of these are about equally toxic or biologically active as the most highly toxic PCDDs. This was reported true for the 2,3,7,8-tetra- and 1,2,3,7,8- and 2,3,4,7,8-penta CDFs.

#### POLYCHLORINATED DIBENZOFURANS (PCDFs)

##### PRESENCE IN PCB PREPARATIONS

Bowes et al. (1975) found PCDFs, tetra-, penta- and hexachloro congeners, in all

PCB preparations analyzed, except Aroclor 1016. They were found to be present at levels totaling from 0.8-2.0 ppm (ug/g) in Aroclor 1248 and two lots each of 1254 and 1260, and at 8.4 ppm in Clophen A-60 and 13.6 ppm in Phenoclor DP-6. Their findings indicate that the Clophen and Phenoclor contained 11 and 17 times more total PCDFs than the comparable Aroclor 1260 (0.8 ppm).

As large amounts of PCBs have entered the environment, it can be assumed that quantities of PCDFs have also been released in proportional amounts.

##### PCDFs IN PCB-CONTAMINATED RICE OIL

PCDFs have been isolated from the PCB-contaminated rice oil that was involved in the 1968 Yusho incident in Japan (Morita et al. 1977). This rice oil was reported to contain from 830-1030 ppm of Kaneclor KC-400, a Japanese PCB very similar to Aroclor 1248 in gas-chromatographic profile (Kuratsune et al., 1976); such rice oil also had a much higher level of PCDFs than the KC-400 by a factor of 250. That is, the pure KC-400 PCB contained 20 ppm of PCDFs and the Yusho oil with ca. 1000 ppm PCBs had 5 ppm PCDFs. This higher level of PCDFs in the rice oil containing "used" PCBs implies that usage of the KC-400 as a heat transfer

medium resulted in increased PCDF formation.

#### OTHER EXAMPLES OF PCDFs IN USED PCBs

Morita et al. (1977) found a 4-fold increase in PCDFs in a PCB used for two years as a heat exchanger.

They also reported an increase in PCDFs when PCBs were heated with air in a sealed glass tube at 300°C for two weeks.

#### VARIETY OF PCDFs WITH VERY HIGH ACUTE TOXICITY

Buser et al. (1978c) found that the Yusho oil contaminated with used PCBs contained more than 40 different PCDFs. They identified 2,3,7,8-tetra- and 2,3,4,7,8-penta-CDF as major constituents, both of which are reported to have very high acute toxicity.

#### Liver Necrosis

As early as 1961 (Bauer et al., 1961), it was shown that a single oral dose of 0.5-1.0 mg/kg of a mixture of tri- and tetra-PCDFs caused severe and often lethal liver necrosis in rabbits; application to the rabbit ear resulted in chloracne (see section on Chloracne). For 2,3,7,8-TCDD, a single oral dose of 0.05-0.10 mg/kg ( $\frac{1}{10}$ th the previous dose) caused a lethal liver necrosis in the rabbit and also caused chloracne when applied to the ear.

#### TCDF: ORAL LD50/30

Moore et al. (1976) reported that the oral LD50/30 (the dose causing 50% mortality in a 30 day period) of 2,3,7,8-TCDF to Hartley guinea pigs was 2.0 ug/kg, which compares quite closely to that of 2,3,7,8-TCDD cited earlier (0.6).

Oral dosage of this TCDF to 1 day old

chicks at 5 ug/kg per day resulted in their death in an average of 11.5 days; at 1 ug/kg/day it was felt by the author that all or most of the chick would have died by 30 days (experiment ended on day 21).

#### PATHOLOGICAL CHANGES

The most striking gross pathological change noted was the accumulation of clear fluid, as indicated by marked subcutaneous edema, ascites (fluid in abdomen), and hydropericardium (abnormal accumulation of serous fluid in the pericardial cavity).

A second pronounced change was a marked decrease in size of the thymus and spleen (*Fig. 3*), found also in the guinea pigs.

Somewhat surprising, oral dose levels of this TCDF up to 6000 ug/kg in C57BL/6 mice or 1000 ug/kg in rats failed to produce any toxic effects. These levels are considerably higher than toxicity induced by TCDD in these species.

#### TCDF STUDIES WITH MONKEYS

Moore et al. (1970) extended these studies to include 2,3,4,7,8-penta CDF and rhesus monkeys. At a 1000 ug/kg (1 mg/kg) oral dosage of 2,3,7,8-TCDF, 2 of 4 monkeys died 25 and 31 days later; at 1500 ug/kg both monkeys died 14 and 23 days after dosing.

#### Delayed Toxic Response and Dose Related

They found the toxic response to be dose related and did not manifest itself clinically until 7-10 days after dosing.

#### Symptoms

Monkeys at this time developed:

- 1) Some facial edema (of the eyelids and lips).



# TRAUMA

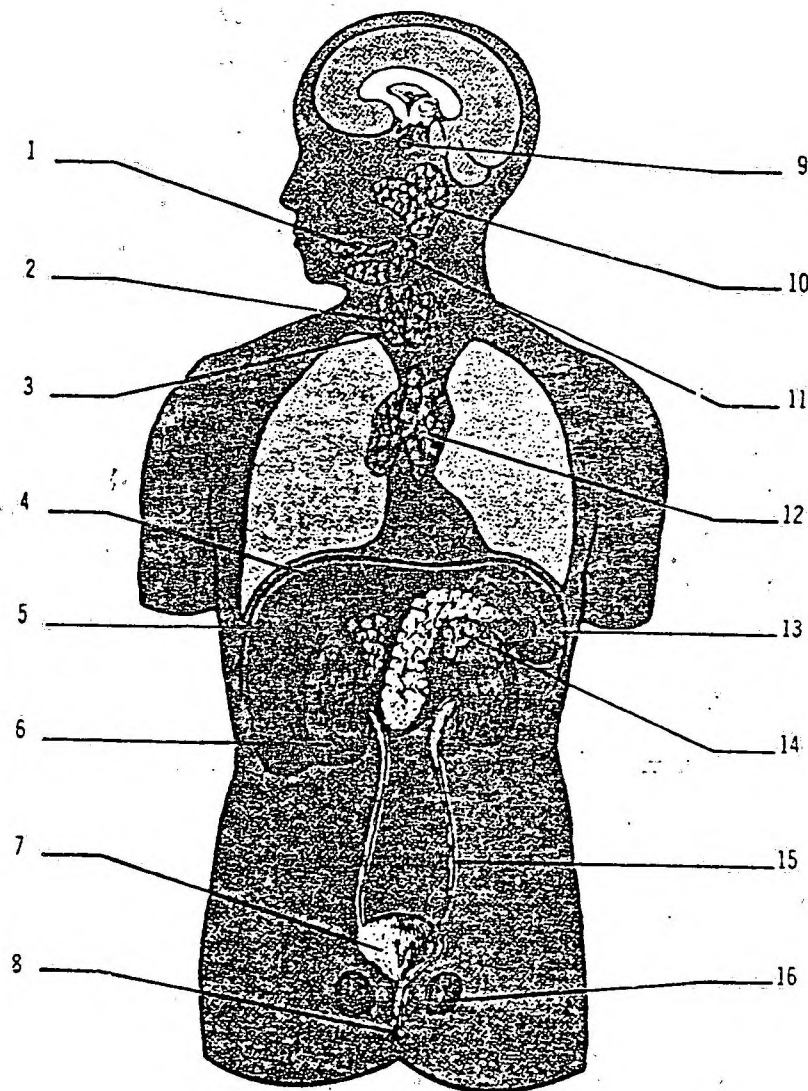


FIG. 3. Endocrine and Salivary Glands; Spleen, Liver, Pancreas; Kidneys and Ureters

Note the thymus gland (12) and the spleen (13), two of the organs of the lymphoid system which contain lymphocytes. The lymphocytes, small white blood cells, are the basis for an animal's (including human's) immune system.

- |                      |                        |
|----------------------|------------------------|
| 1) Sublingual gland  | 9) Pituitary gland     |
| 2) Thyroid gland     | 10) Parotid gland      |
| 3) Parathyroid gland | 11) Submaxillary gland |
| 4) Pancreas          | 12) Thymus gland       |
| 5) Liver             | 13) Spleen             |
| 6) Kidney            | 14) Adrenal gland      |
| 7) Urinary bladder   | 15) Ureter             |
| 8) Urethra           | 16) Gonad              |

- 2) Anorexia.
- 3) Occasional vomiting and depression.
- 4) Loss of facial hair, especially the eyelashes.

Loss of toenails and fingernails occurred also and the skin developed a dry leathery texture (hyperkeratosis).

#### *Clinical Pathology*

Clinical pathology included mild anemia, consistent lymphopenia (decrease in blood lymphocytes), marked neutrophilia (increase in blood neutrophil leukocytes), a 33-50% decrease in serum cholesterol, and moderate decreases in total serum proteins and serum albumin.

#### *Post-Mortem Findings*

Post-mortem examination indicated a spectrum of lesions in the treated monkeys which reflected the clinical findings above. These included a moderate to severe loss of body fat, enlarged bile ducts, hyperemia (excess of blood in parts), scattered areas of petechial (pinpoint spots) hemorrhage, facial ulceration and small bubble-like cysts in the fundic and duodenal areas of the stomach and proximal small intestine.

Cutaneous, eyelid, external ear canal and toe nail lesions were apparent in all animals.

Atrophy of the thymus and spleen (*Fig. 3*) were pronounced at the 1500 ug dosage, but no liver lesions were observed. Hyperplastic changes were noted in the bile duct and gall bladder epithelium and a degranulation of exocrine pancreatic cells.

The authors established that the LD<sub>50</sub>/60 of 2,3,7,8-TCDF for rhesus monkeys as 1000 ug/kg, a dose that is about 20 fold higher than that estimated for 2,3,7,8-TCDD (McConnel et al., 1978).

#### *TCDF STUDIES WITH GUINEA PIGS*

Moore et al. (1979) in this paper reported the acute oral LD<sub>50</sub> to guinea pigs of this TCDF to be > 5 and < 10 ug/kg and for the 2,3,4,7,8-PCDF to be > 3 and < 10 ug/kg, indicating that both PCDFs are extremely toxic in a single dose to guinea pigs.

At necropsy, they found no difference in the pattern of lesions to guinea pigs for TCDF or PCDF. They cited a marked reduction in thymus size, lack of body fat and reduced muscle mass. Histopathology revealed a loss of lymphoid cells in the thymic cortex and hyperplasia (abnormal increase in cell numbers or arrangement) of epithelial cells in the renal pelvis, ureter, and urinary bladder.

These and other lesions not cited were similar to those described in guinea pigs poisoned by TCDD (Gupta et al., 1973).

An LD<sub>50</sub> value has not yet been established for TCDF in the rat or mouse, although some toxic signs were noted at 1-10 mg/kg body weight (Moore et al., 1976, 1979; Birnbaum et al., 1980).

#### *DISPOSITION OF TCDF IN BODY OF TEST ANIMALS*

Birnbaum et al. (1981) found that TCDF disposition in monkeys is similar to that in rats, but monkeys clear TCDF from the body more slowly than do rats and are therefore more sensitive to TCDF intoxication.

In guinea pigs, Decad et al. (1981), found, after 6 or more weekly doses of TCDF at 1 ug/kg, that TCDF was accumulated in the liver, adipose and skin.

When a body burden of only 5.6-6.6 ug/kg was attained, they found that the toxicity of this compound was irreversible and

resulted in progressive weight loss and death. The reason mice, and perhaps rats, are more resistant to TCDD has been suggested in studies by Nagayama et al. (1980). They found that more than 80% of PCDFs given orally to mice were eliminated rapidly thus minimizing absorption. Intraperitoneal dosing, bypassing the digestive tract, resulted in very high liver accumulation.

## PROBLEMS IN ASSESSING TOXICOLOGICAL STUDIES

### HIGH TOXICITY OF CONTAMINANTS TO SEVERAL ANIMAL SPECIES

The very high toxicity of several PCDFs to several animal species (guinea pigs, rabbits, chickens, and monkeys) point up the concern induced by findings of these chemicals in commercial PCBs and at higher levels in "used" PCBs. Their presence has made it difficult to assess the many toxicological studies done if this contaminant problem was not addressed directly. Other concerns follow.

### CHLORACNE

The PCDFs also are known to induce chloracne (see Chloracne section), a cutaneous effect where inflammatory changes in the skin occur due to plugging and rupture of the sebaceous glands (McConnel and Moore, 1979) and can be a very long lasting lesion (Urabe et al., 1979). Chloracne is one of the first signs of intoxication from chronic exposure.

### PCDFs TRANSFERRED ACROSS PLACENTA AND THROUGH MILK: ACCUMULATION IN LIVER

Nagayama et al. (1980) fed a mixture of seven PCDFs at 0.6 ppm in the diet to mice

for 18 days after mating or for 14 days after delivery. They found that PCDFs were transferred across the placenta to the fetuses and to the offspring in milk. The amounts transferred through milk were much larger than across the placenta. The liver was the greatest site for accumulation of PCDFs. This is in marked contrast to the PCBs which preferentially are sequestered in adipose tissues. Both 2,3,7,8-tetra- and 2,3,4,7,8-penta-CDFs were found in the suckling mice and accumulated in the liver of the dams.

### PCDFs IN TISSUES OF YUSHO PATIENTS

PCDFs have also been found in the tissues of patients with Yusho from Japan. Nagayama et al. (1977) reported finding 2,3,6,8- and 2,3,7,8-tetra- and 1,2,4,7,8- and 2,3,4,7,8-penta-CDFs and a hexa-CDF as well as PCBs in tissues of Yusho patients, but only PCBs in normal patients.

It is noteworthy that some PCDFs, especially 2,3,4,7,8-penta-CDF, were still present in the tissue of patients more than 9 years after the Yusho incident.

### Toxic Effects to Liver

This penta-CDF plus 2,3,7,8-CDF were reported by Poland et al. (1976) to be among the most toxic PCDFs and to be bound strongly to hepatic cytosol proteins and to be powerful inducers of the liver enzyme, arylhydrocarbon hydroxylase. The highly toxic TCDD also induces this enzyme (Goldstein et al., 1978); and because of this and their similar patterns of toxic effects, suggests a similar mechanism of action (Moore et al., 1979). It is therefore prudent to consider the toxic potential of the PCDFs and the PCNs (following section) in assessing the toxicity of PCBs.



## POLYCHLORINATED NAPHTHALENES (PCNs)

### SOURCE OF PCNs IN PCB MIXTURES

The PCNs found in PCB mixtures undoubtedly resulted from the presence, in small amounts, of naphthalene in the original biphenyl used to manufacture the PCB.

### COMMERCIAL USES OF PCNs

PCNs are also commercially available industrial chemicals marketed in the U.S. by the Koppers Co. under the tradename Halowax. They have a wide variety of suggested uses related to their electrical, flame retardant, and fungus-resistant properties, stability and compatibility with other materials (Anonymous, Undated). The PCNs have been used as:

- 1) Boat hull coatings, because of their antimagnetic properties.
- 2) In the electronics, radio and television industries as insulating waxes, sealing compounds, and dielectrics for condensers.
- 3) High pressure lubricant additives.
- 4) Wood preservatives (Taylor, 1979).

### ANIMAL STUDIES OF PCN TOXICITY

The finding of hexa- and heptachloro PCNs in commercial PCBs is significant.

#### X-Disease in Cattle

Bell (1952), studying the mysterious X-disease in cattle, later called bovine hyperkeratosis (hypertrophy of the corneous layer of the skin), induced by a lubricant, identified the toxic factor in the lubricant as a highly chlorinated naphthalene. He found that toxicity of PCN in cattle was produced by a total dose of 1.0 mg/kg of body weight given during a 7-day period.

At this dose, signs of intoxication appeared on the 12th day after administration began.

Bell (1953) in testing different PCNs found that hexachloronaphthalene was the most toxic, with hepta- > octa- > penta- > tetra- > di- and tri-chloronaphthalenes next. With hexa-PCN, five calves developed symptoms by the 5th day after oral administration and all came to autopsy by day 15-29 after receiving total doses of 0.5-4.6 g in small doses over several days. Symptoms included lacrimation, nasal discharge, salivation, red areas on oral mucosa, anorexia, depression, indentation of horn and finally extreme weakness or prostration. Chronic intoxication in cattle produced cutaneous hyperkeratosis and an excessive drop in vitamin A level.

#### Study of Sheep

Brock (1959) found sheep to be 10 times more resistant than cattle. Sheep fed 1.1, 11, or 27.5 mg/kg body weight of Halowax 1014, a mixture of tetra-, penta- and hexachloronaphthalene, died on average after 106, 27, or 20 days, respectively. About 4 g of this PCN was the smallest lethal dose to sheep.

### PCNs CONTRIBUTE TO TOXICITY OF PCBs

These data indicate the relative toxicity of PCNs to two animals and give an indication that they too can contribute to the toxicity found for PCBs, as will be covered later. The historical coverage of PCNs from an industrial exposure setting can be found in NIOSH (1977) and EPA (1975) has reviewed their hazard potential.

## RESTRICTIONS IN USE OF PCBs

Japan prohibited the production of PCBs in 1972 in light of the health implica-

tions of exposure and the earlier "Yusho" human poisoning incident (IARC, 1978). In the United Kingdom, PCB manufacturers sell PCBs only when used in dielectric fluids while in West Germany manufacturers can sell PCBs only as dielectric, heat-transfer and hydraulic fluids (IARC, 1978). Switzerland and Sweden since 1972 have restricted PCB sales to heavy industrial use with authorization (IARC, 1978).

Monsanto limited U.S. sales of PCBs in 1971 to use in closed systems, and in 1972 discontinued sales for heat-transfer application (IARC, 1978), and all production of PCBs ceased in October 1977 (NAS, 1979).

On 2 February 1977, EPA issued regulations prohibiting PCB manufacturers and transformer and capacitor producers from discharging PCBs into waterways; the PCB level in ambient water was limited to 0.001 ug/l (EPA, 1977).

## TOXIC SUBSTANCES CONTROL ACT

The demise of PCB production was signaled by the passage on 11 October 1976 of Public Law 94-469, the long sought for Toxic Substances Control Act. Section 6(e) of TSCA specifically:

- 1) Prohibits production of PCBs in the U.S.
- 2) Regulates disposal of PCB contaminated materials.
- 3) Restricts the use of such materials already in service (NIOSH, 1977).

The net effect of this law should be to eliminate releases of PCBs into the environment and, eventually, to reduce existing environmental PCB levels.

## ENVIRONMENTAL LEVELS CANNOT BE REDUCED FOR MANY YEARS

Due to the extreme stability of PCBs, however, environmental levels will not be reduced substantially for many years, and the problem remains of dealing with existing PCB reservoirs in the environment (NAS, 1979).

## PERMITTED EXPOSURE OR RESIDUE LEVELS

### OSHA STANDARDS

OSHA (U.S. Occupational Safety and Health Administration) has published standards which require that employee's exposure to PCBs containing 42% chlorine (Aroclor 1242) cannot exceed an 8-hour time-weighted average (TWA) of 1 mg/m<sup>3</sup> and exposure to PCBs of 54% chlorine (Aroclor 1254) cannot exceed a similar TWA of 0.5 mg/m<sup>3</sup> for any 8-hour shift of a 40-hour work week (OSHA, 1977).

In the USSR and East Germany (GDR) these values are 1.0 mg/m<sup>3</sup> for both, in Sweden 0.5 mg/m<sup>3</sup> for both, and in West Germany (FRG) and Czechoslovakia are the same as in the U.S. (Winell, 1975).

### FDA: PCB RESIDUE LEVELS IN FOOD PRODUCTS

The FDA (U.S. Food and Drug Administration) in April 1977 set lower tolerance (residue) levels of PCBs in various food products to reduce human exposure (FDA, 1977).

Milk and dairy products (fat basis) were reduced from 2.5 to 1.5 ug/g (parts per million; ppm); in poultry (fat basis) from 5 to 3 ppm; in eggs from 0.5 to 0.3 ppm; in fish and shellfish from 5 to 2 ppm.

Tolerance levels left unchanged were:

infant and junior foods, 0.2 ppm; in finished animal feeds, 0.2 ppm; in animal feed components, 2.0 ppm; and in food-packaging paper materials without a PCB barrier, 10 ppm. These data may not reflect the most recent situation since such regulations are constantly subject to change. It should not be implied that other countries do not have similar regulations.

## ROUTES AND RATES INTO ENVIRONMENT

With about 1,000,000 tons of PCBs produced worldwide from 1929 through 1977, about half still in service and the other half in various environmental compartments, how did they get into the environment? Since initial studies indicated very low acute toxicities, there was little concern over possible environmental/human exposure except in industrial/occupational settings.

## POSSIBLE ROUTES

As with most industrial chemicals, loss figures for PCBs are essentially non-existent. A primarily qualitative assessment of rates and routes of PCBs into the environment has been made by Nisbet and Sarofim (1972). They list the possible routes into the environment to include:

- 1) Leaks from heat exchangers and sealed transformers.
- 2) Leaks from hydraulic systems of fluids containing PCBs.
- 3) Losses and spills of PCB fluids during manufacture.
- 4) Improper disposal of PCB-containing fluids or waste PCBs.
- 5) Leaching or volatilization from PCB-containing formulations.

## INCINERATION OF WASTE PRODUCTS

A sixth could be added which would be volatilization of PCBs during incineration of waste products in small commercial, municipal or domestic incinerators and from open-burning dumps where temperatures are too low or residence time too short. A residence time of 2 seconds at 2000°F is recommended (Nisbet and Sarofim, 1972).

## ENVIRONMENTAL LOSSES

These authors estimate annual environmental losses to be:

- 1) 1,500-2,000 tons into the atmosphere.
- 2) 4-5,000 tons into fresh and coastal waters.
- 3) 18,000 tons into dumps and landfills.

## SOURCES OF PCBs

From their data, they estimate that only about 20% of 1970 sales in North America, some 7,000 tons, represented a net increase in the amount of PCBs in use in transformers, capacitors and heat exchangers.

The remainder (almost 30,000 tons; see Table 3) was assumed to have been discharged into the environment with:

22,000 tons by disposal in dumps, landfills and incinerators.

1-2,000 tons by evaporation of plasticizers.

4-5,000 tons by leaks and disposal of hydraulic fluids and lubricants plus small quantities by disposal of heat transfer and transformer oils.

They estimate only 10-20% (ca. 3,000 tons) were destroyed by burning.

The NAS (1979) report estimated (page 6) that total cumulative PCB use from U.S. sources through 1975 as 683,000 tons, and



losses of PCBs which entered the *mobile* environmental reservoir based on production and use data, to have been over 90,000 tons. Converting this figure to pounds, 180,000,000 lbs., gives one a better perspective of total environmental pollution.

#### WHERE DID WASTE PCBs GO BEFORE 1972?

Nisbet and Sarofim (1972) pointed out the problem of what became of scrap or waste PCBs by reporting that Monsanto in 1971 set up a disposal system for their customers, and within a year of announcement of this service, 500,000 lbs. of waste PCBs had accumulated at the disposal site pending completion of an approved incinerator. The question that remains is where did these waste PCBs go before? Much of it undoubtedly went into sewers, waters, and dumps and landfills.

The problems of disposal and environmental pollution have been stupendous. Hopefully, the passage in 1976 of the Toxic Substances Control Act has rectified these problems and we can concentrate on improving the situation.

#### DESTRUCTION AND DISPOSAL OF PCBs

##### CRITERIA FOR SAFE COMPLETE DESTRUCTION OF PCB

PCBs and PCB-bearing materials can safely be destroyed by incineration, but kiln temperature and residence time are important criteria in assuring complete destruction. Nisbet and Sarofim (1972) report that municipal incinerators which meet design guidelines of a residence time of 2 seconds at 2000°F are necessary to preclude the vaporization of PCBs during incineration.

#### PRESENCE OF PCDDs AND PCDFs IN FLY ASH AND FLUE GAS

Olie et al. (1977) reported the presence of PCDDs and PCDFs in the fly ash and flue gas from municipal incinerators in the Netherlands but no quantitative data are given. In Switzerland, Buser and Bosshardt (1978) found the total amounts of PCDDs and PCDFs in the fly ash to be 0.2 and 0.1 ppm, respectively and in fly ash from an industrial heating facility 0.6 and 0.3 ppm, respectively. The number of individual isomers and congeners was quite large; as many as 30-40 isomers/congeners of PCDDs and PCDFs were found. In other studies (Buser et al. 1978b and c), it was shown that in fly ash the extremely toxic PCDDs (2,3,7,8-tetra- and 1,2,3,7,8-penta-CDDs) are present in minor amounts, but the highly toxic PCDFs (2,3,7,8-tetra- and 2,3,4,7,8-penta-CDFs) are the major constituents.

#### UNCONTROLLED BURNING AS SOURCE OF HAZARDOUS PCDFs

Buser et al. (1978a) found that pyrolysis of technical PCBs yielded about 30 major and more than 25 minor PCDFs, with 2,3,7,8-tetra-CDF, the most toxic PCDF, being one of the main constituents. The yield of PCDFs, considering the amount of PCB recovered and the pyrolysis temperature, was between 3-25% calculated on the amount of PCB decomposed. These results indicate that uncontrolled burning of PCBs can be an important environmental source of hazardous PCDFs.

When comparing the PCDF pattern in fly ash and the pyrolysis of commercial PCBs, there is a striking similarity which suggests that PCBs are the precursors of the PCDFs found in fly ash. This also

points out that destruction of PCB-containing wastes in incinerators must be carefully controlled.

#### EXAMPLE OF BUILDING CONTAMINATION FROM CRACKED TRANSFORMER IN ELECTRICAL FIRE

A serious incident occurred in Binghamton, New York in the early morning of 5 February 1981 when an intensely hot electrical fire adjacent to a transformer pyrolyzed an estimated 90 gallons of Askarel fluids when the transformer cracked (Schecter et al., 1981). The Askarel contained 65% Aroclor 1254 and 35% chlorinated benzenes (mainly tri- and tetrachlorobenzene), and when pyrolyzed spread throughout the 18-story structure as a fine oily soot. Surface swabs of open office spaces yielded an average of 162 ug/m<sup>2</sup> of Aroclor 1254, and two composite soot samples yielded levels of 2.8 and 2.9 ppm 2,3,7,8-TCDD and 273 and 124 ppm of 2,3,7,8-TCDF. The TCDD ("dioxin") was thought to arise from the chlorinated benzenes and the TCDF from the PCBs. Cleanup of the building was suspended when the high concentrations of TCDD and especially TCDF were found.

#### CHANGING RULES FOR DESTRUCTION AND DISPOSAL OF PCBs

One of the prime problems in destruction and disposal of PCBs is that the ground rules keep changing. Current EPA regulations (Sept. 1980) prescribe that substances contaminated with more than 500 ppm of PCBs are to be destroyed in special incinerators. (Anonymous, 1980a). Materials with 50 to 500 ppm may be buried in chemical waste landfills or burned in special high-efficiency boilers.

#### APPROVAL OF INCINERATORS AND LANDFILLS

Both incinerators and landfills have to be approved by EPA, and approvals are slow and fraught with delays.

As of September 1980, EPA had approved only three non-commercial incinerators for private on-site plant use (Anonymous, 1980b); one approved in late 1979 was on General Electric property at Hudson River, N.Y. (Anonymous, 1979). This reference cited a listing by EPA of eight landfills for disposal of large PCB-containing capacitors; but on March 1, 1981, EPA banned capacitor landfilling after ENSCO (Engineering Specialities Co.) of El Dorado, Arkansas gained approval January 1981 for its commercial capacitor incinerator (Anonymous, 1981a). It was reported that ENSCO had a capability of about 17,500 capacitors/month with an estimated 20,000 capacitors/month being removed from service. A second commercial incinerator approved by EPA in January 1981 was that of Rollins Environmental Services of Deer Park, Texas (Anonymous, 1981b); test burns in 1979 of oils containing 47 and 80% PCBs for ENSCO and Rollins, respectively, destroyed greater than 99.999% of the PCBs.

#### CAPACITOR TREATMENT SYSTEM

A second capacitor treatment system was approved for Environmental International, Inc. of Kansas City, Kansas by EPA Region VII (Anonymous, 1982). This firm was purchased in April 1982 by Chemical Waste Management of Chicago, which owns the Vulcanus incinerator ship. This latter company received a six-month EPA permit to burn 3.6 million gallons of PCB-laden liquids at sea using the Vulcanus, which left port in December 1981 to con-

duct a five-day shipboard test burn of 500,000 gallons of oil containing more than 500 ppm PCBs (Anonymous, 1981c & d).

#### CHEMICAL PROCESSES FOR PCB DESTRUCTION

There are several chemical processes for PCB destruction. Acurex Waste Technologies of Mountain View, Calif., as of March 1982, has EPA approval for its proprietary portable chemical detoxification system in Regions I, V, VI and VII. Sunohio of Canton, Ohio has another process called PCBX which uses a proprietary reagent to strip away chlorine atoms to form harmless residues and restores the oil for re-use free of PCBs (Anonymous, 1980a). Goodyear Tire and Rubber Co. uses sodium naphthalide as the reagent to strip chlorines off and form sodium chloride (Anonymous, 1980b). Other technologies also are being investigated.

The American Chemical Society held a two-day symposium in New York on August 24-25, 1981, entitled "Detoxification of Hazardous Wastes," where a number of the above processes were discussed.

#### HEALTH EFFECTS

This section will include a discussion of the following:

- 1) Chloracne.
- 2) Various effects of the human poisonings in Japan and Taiwan.
- 3) Human residues.
- 4) Enzyme induction and its effects.
- 5) Immune effects.
- 6) Lung effects.
- 7) Reproduction and endocrine effects.
- 8) Neurological and behavioral effects.
- 9) Liver effects.

#### CHLORACNE

Chloracne, one of the first signs of intoxication from PCBs or its impurities, is a skin disorder described as a refractory follicular dermatosis produced by environmental exposure to certain halogenated (halogen refers to any of the four very active, non-metallic elements—chlorine, bromine, iodine and fluorine) aromatic (denoting a compound characterized by a benzene ring) compounds, which may be accompanied by systemic toxicity (Taylor, 1974).

#### FROM OCCUPATIONAL AND NON-OCCUPATIONAL EXPOSURES

Initially just an industrial problem, first observed in 1897, most cases up to World War II involved exposures to PCNs and PCBs; but new outbreaks of the disorder have occurred and include non-industrial populations exposed to these and other halogenated chemicals such as PCDDs, PCDFs, brominated biphenyls and benzofurans, and contaminants in various herbicides (Taylor, 1979).

Chloracne has been reviewed also by Crow (1970) and Von Weirich (1978). An early history of occupational Chloracne due to PCBs and PCNs can be found in NIOSH (1977). Chloracne is also one of the most constant and prominent features of exposure to 2,3,7,8-TCDD ("dioxin") (IARC, 1977).

#### PCN FUMES MOST POTENT CHLORACNEGEN

Crow (1970) has concluded that for the PCNs, fumes are the most potent chloracnegens, solutions less so, and solids rarely cause chloracne.

Shelly and Kligman (1957), in human



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studies, reported that penta- and hexa-PCNs were potent acnegens (substances that cause acne), whereas tri-, tetra-, hepta-, and octa-PCNs were not. As mentioned earlier, hexa-PCNs were found as contaminants in PCBs and may add to the toxicity syndrome picture of the PCBs.

Von Weirich (1978) reported that the tri- and tetra-CDFs are both potent chloracnegens and hepatotoxins (toxins affecting the liver), and the penta- and hexa-CDFs are also potent acnegens.

### CHANGES IN SEBACEOUS GLANDS

Chloracnegens, such as the PCBs, PCNs, PCDFs or PCDDs, cause changes in the sebaceous glands (glands of the skin, secreting an oily substance, sebum), as observed clinically in monkeys by the cutaneous, eyelid and auditory lesions found (McConnell and Moore, 1979). These changes resulted from a metaplastic change to a squamous-type epithelium that alters the character of the gland secretions from normal oily to keratinous (of the nature of keratin, an albuminous substance forming the principal matter of hair, nails, horn, etc.), resulting in a dry skin and blepharitis (eyelid inflammation). This often results in plugging and rupturing of the glands with inflammatory changes (chloracne). Concurrently with these lesions, hyperkeratosis (overgrowth of the corneus layer of the skin) of the hair follicles often occur. A similar pathogenesis of chloracne-like lesions is observed in rabbits.

### INITIAL SYMPTOMS IN YUSHO DISEASE

Initial symptoms experienced by 136 patients with "Yusho" were increased eye discharge and swelling of upper eyelids (blepharitis) (38.3%), followed by acne-

form eruption (chloracne) and follicular accentuation (33.1%), and pigmentation of the skin (9.6%) (Kuratsune et al., 1972).

### DERMAL CONTACT, INHALATION OR INGESTION

Although chloracne typically occurs from external dermal contact, inhalation or ingestion can be important as the Yusho example illustrates for ingestion.

### PERSISTENCE OF CHLORACNE

Chloracne was reported by Taylor (1974) to persist for as long as 15 years after exposure terminated. By 1975, the mucocutaneous lesions of Yusho victims poisoned in 1968 showed improvements in only 64% of the patients (Urabe et al., 1979). By 10 years post-outbreak (1978), these lesions were greatly improved but have been superseded by systemic disorders. The paper by Umeda (1972) contains photographs of Yusho victims with chloracne which dramatically demonstrate the lesions.

## HUMAN POISONINGS

Two PCB poisoning episodes involving thousands of people eating PCB-contaminated cooking oil have occurred in the Far East and provide us with data on the effects of PCBs on the human animal. The first incident occurred in Japan on the southwestern island of Kyusho in Fukuoka Prefecture in 1968. The second episode occurred in Taiwan in 1979 and data on this incident are still fragmentary.

### YUSHO DISEASE

#### OUTBREAK OF SKIN DISEASE

This first episode in Japan had its beginnings in March 1968 when an epidemic

## TRAUMA

of a peculiar skin disease similar to chloracne was reported in Fukuoka Prefecture which later spread to over 20 other prefectures in western Japan (Kuratsune et al., 1972). After clinical and chemical analyses, in August 1968, it was determined that the disease was induced by organic chlorides, and in November 1968 that the specific cause of the disease was rice oil contaminated with Kanechlor 400 (KC-400), similar to Aroclor 1248 (Umeda, 1972).

### MINIMUM AND AVERAGE CONSUMED DOSE

The concentration of KC-400 in the rice oil was 2,000-3,000 ppm and the average consumption of contaminated rice oil was about 800 ml, making the average ingestion of C-400 to be about 2 grams (g) (28 grams to an ounce) (Kuratsune et al., 1972). The minimum dose of KC-400 consumed was estimated to be about 0.5 g. The disease was called "Yusho" or oil disease.

### NUMBER OF VICTIMS

By August 1971, there were 1057 patients (Kuratsune et al., 1972); but by the end of 1977, the victims numbered 1665 (Urabe et al., 1979). Umeda (1972) claims there are an estimated 15,000 victims of the disease but far fewer have been "officially" diagnosed as having Yusho. The most highly contaminated rice oil was traced back to its origin in being produced or shipped on February 5 and 6, 1968 (Kuratsune, 1976).

### SYMPTOMS OF FOUR TYPES OF "YUSHO" DISEASE

Umeda (1972) revealed there are four types of the disease:

- 1) Latent.
- 2) Visceral.
- 3) Manifest.
- 4) Tardive.

In the *latent* type, the patient has no significant physical nor subjective symptoms of Yusho. Examples of this type were apparent from women without symptoms who gave birth to babies displaying typical symptoms and women who breast-fed babies whose babies displayed pathological symptoms in six months or later.

The *visceral* type has no characteristic dermatological signs but displays visceral symptoms such as:

- 1) General fatigue.
- 2) Nausea or vomiting.
- 3) Mild jaundice.
- 4) Abdominal pain (colic-like).
- 5) Diarrhea.
- 6) Productive cough.
- 7) Chronic bronchitis.
- 8) Asthmatic attacks or pneumonia.

The *manifest* type is the typical Yusho victim with chloracne, comedo-like (like blackheads) eruptions and follicular accentuation of the skin.

Other symptoms include:

- 1) Dark-brown pigmentation of the skin and nails and of the mucous membranes of the eyes and mouth.
- 2) Hypersecretion of cheese-like discharge from the eyes.
- 3) Loss of hair.
- 4) Loss of libido.
- 5) General fatigue.
- 6) Headache.
- 7) Stomachache.
- 8) Numbness of the extremities.
- 9) Nausea, vomiting.
- 10) Dizziness.

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- 11) Disturbances of higher nervous activities (e.g., forgetfulness).
- 12) Local impairment of blood circulation.
- 13) Deformation of nails.
- 14) Deformities of joints and bones (fingers, toes, ankles and wrists).
- 15) Poor teeth development in children.
- 16) Pathological changes in teeth.

The *tardive* type is a delayed appearance of physical signs and symptoms specific to Yusho which appear one to three years after exposure. The photos in this report visually present the manifest type of Yusho.

### CHICKEN POISONING FROM OIL-CONTAMINATED FEED PRECEDED YUSHO INCIDENT

It should be mentioned that in February-March 1968, an accidental mass poisoning of over 2 million chickens, with over 400,000 reported as dying, occurred in western Japan (Kuratsune et al., 1972). Its cause was traced to a dark oil used in the chicken feed which was found to contain 1,300 ppm Kanechlor 400. This oil was from the same company involved in the Yusho incident. This epizootic among chickens and the epidemic of Yusho had been very closely connected in time, although the chicken episode preceded the Yusho incident in severity by several months.

### CLINICAL FINDINGS

The main clinical findings of Yusho patients concern dermatosis. Major cutaneous changes include:

- 1) Acneform eruptions.
- 2) Prominent enlargement and elevation of the follicular openings.

- 3) Pigmentation and flattening of the nails.
- 4) Skin pigmentation (Kikuchi and Masuda, 1976).

These cutaneous lesions are described in detail by Urabe and Koda (1976).

### AUTOPSY FINDINGS

Kikuchi and Masuda (1976) reviewed the autopsy findings of five Yusho patients and one stillborn child born to a Yusho mother. They found that PCB concentration rates in the autopsy cases exhibited no definitive differences from control cases suggesting that the cutaneous changes found might be residual effects occurring at the acute or subacute toxic stage.

Autopsies were performed 12-46 months after the first appearance of skin lesions; and apart from the skin lesions, no definitive changes in the visceral organs were seen.

Amounts of KC-400 ingested in these cases were not known exactly except in one where ingestion of 1.6 g of KC-400 was estimated.

### NON-DERMAL MANIFESTATIONS OF PCB POISONING

Apart from the cutaneous changes noted, non-dermal manifestations of PCB poisoning included the following disorders:

- 1) Neurologic.
- 2) Endocrine.
- 3) Respiratory.
- 4) Hematologic.
- 5) Hepatic.
- 6) Metabolic.
- 7) Bone and joint.
- 8) Dental.
- 9) Ophthalmic.



- 10) Effects on infants and children (Hirayama, 1976).

#### *Neurological Disorders*

For neurologic disorders, about 50% of Yusho patients complained of headaches, numbness, hyposthesia (dulled sensation), and neuralgic limbs. Clinical observations suggest that there are no significant involvements of the central nervous system, but rather of the peripheral nerves and almost exclusively, sensory nerves (Hirayama, 1976).

#### *Endocrine Disorders*

Endocrine disorders suggest some degree of adrenocortical dysfunction and abnormal ovarian function in females. This latter point may be due to enhanced degradation of sex hormones by enzymes induced by PCBs. This is discussed later.

#### *Respiratory Disorders*

Respiratory disorders appear to be exemplified by chronic bronchitis. Following ingestion of PCBs, most PCBs enter the blood stream via the thoracic duct and hence reach the respiratory system and have been detected in the lung and sputum of patients (Hirayama, 1976). The cause of bronchitis seems obscure, but the PCBs appear to affect some defense mechanism.

#### *Hematological Disorders*

Hematology findings correspond to the features of inflammatory disorders (Hirayama, 1976). Serum levels of immunoglobulins, especially those of IgA and IgM were decreased generally, suggesting B cell lymphocyte dysfunction. The B cells are responsible for humoral immune responses based on antibodies. Chronic infections observed generally in patients may be the

result of some immunological deficiency. This will be detailed later.

#### *Liver Disorders and Enzyme Alterations*

Hepatic disorders observed are related directly to the fact that the PCBs are known to be powerful inducers of liver enzymes, especially the microsomal drug-metabolizing enzymes (mixed-function oxidases, MFO) and mitochondrial -amino-levulinic acid, ALA) synthetase. This microsomal enzyme induction results in an increased rate of metabolism of both endogenous substances, such as hormones, and xenobiotic substances, such as drugs and pesticides.

#### *Degradation of Hormones and Menstrual Disorders*

Since PCBs cause increased degradation of hormones, including estradiol, a decrease in circulating estradiol may be responsible for the menstrual disorders seen in female Yusho patients (Hirayama, 1976).

The enzyme ALA-synthetase is the first and rate-limiting enzyme in the biosynthetic pathway of heme (constituent of hemoglobin) (Woods, 1973) and could lead to an overproduction of porphyrins (important chemical substances which form the basis of the respiratory pigments of animals and plants, hemoglobin is the respiratory pigment of the blood) by the liver resulting in porphyrinuria (Poland and Glover, 1973).

Related to this enzyme induction were the liver findings of a marked proliferation in the smooth endoplasmic reticulum and morphological heterogeneity (i.e., variations in size and form) of the mitochondria with some patients showing a slightly enlarged liver (hepatomegaly) (Hirayama, 1976).

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### Metabolic Disorders

Metabolic disorders center around alterations in general lipid (fat) metabolism probably as a result of PCB concentration in adipose tissue or skin, the latter leading to cutaneous manifestations already discussed, the former resulting in elevated serum triglycerides (Hirayama, 1976).

Other findings suggest abnormal calcium metabolism resulting in the bone and dental disorders mentioned which may result from vitamin D deficiency caused indirectly by enzyme induction noted above (Hirayama, 1976).

### TOXIC IMPURITIES IN PCB

As discussed earlier under Toxic Impurities, the presence of toxic PCDFs in KC-400, and even more so in the Yusho oil, make evaluation of Yusho toxicity on a cause and effect basis very difficult. Kuratsune et al. (1976) reported the presence of PCDFs in the fat of tissues of Yusho patients of autopsy. These data are condensed and rearranged in Table 9.

As mentioned earlier, the ratio of PCBs to PCDFs in the Yusho rice oil was about 200; but in these autopsy cases, the liver has shown a pronounced persistence and

hence concentration of PCDFs. Of these PCDFs, 2,3,4,7,8-penta-CDF was the most abundant found by Masuda et al. (1982) in rice oils of both the Taiwan and Japan poisoning episodes; and Kuroki and Masuda (1978) reported it to be one of, if not the most accumulative of the PCDFs in humans. This accumulative factor deserves closer scrutiny.

### TAIWAN POISONING EPISODE

The second, large-scale human poisoning episode by PCBs occurred in central Taiwan in March 1979, 11 years after the Yusho incident, with reports of a peculiar skin disease (Chen et al., 1980).

### CAUSE AND NUMBER OF VICTIMS

In October the cause was identified as being due to ingestion of rice oil contaminated with PCBs, an almost exact replica of the Yusho accident; and by May 1980, the victims numbered 1900. These authors found that the PCB ingested was closer to KC-500 and thus would have higher levels of more highly chlorinated PCBs (penta- to heptachlorobiphenyls), and these would be expected to be more persistent.

Table 9

PCBs AND PCDFs IN PPM (FAT BASIS) OF TISSUES OF YUSHO PATIENTS AT AUTOPSY

| Year of Death | Case No. | ADIPOSE |       | Ratio PCB/PCDF | LIVER |       | Ratio PCB/PCDF |
|---------------|----------|---------|-------|----------------|-------|-------|----------------|
|               |          | PCBs    | PCDFs |                | PCBs  | PCDFs |                |
| 1969          | 1        | 3.4     | 0.03  | 113            | 4.7   | 2.3   | 2              |
| 1969          | 2        | 8.5     | 0.04  | 213            | 5.6   | 1.1   | 5              |
| 1972          | 3        | 2.1     | 0.01  | 210            | 3.5   | 0.3   | 12             |
| Mean          |          | 4.7     | 0.03  | 157            | 4.6   | 1.2   | 4              |

## COMPARISONS OF CONTAMINATED RICE OILS

Masuda et al. (1982) compared the PCBs in the two rice oils causing these two poisonings. They found the rice oil from Taiwan (two samples) to contain 60 and 100 ppm of PCB while the Japanese rice oil analyzed contained 900 ppm PCB. The difference was that the Taiwanese samples were more similar to KC500 (54% chlorine) while the Japanese sample was similar to KC-400 (48% chlorine). They also found several PCDFs totaling 2.02 ppm in the Japanese and 0.08 and 0.10 ppm in the Taiwan samples.

PCQs AS ADDITIONAL CONTAMINANT  
IN RICE OILS

An interesting recent discovery, highlighted in the paper by Masuda et al. (1982), was the presence of polychlorinated p-quarterphenyls (PCQs) and PCQ ethers in both the Japanese and Taiwan rice oils. The PCQs contain four phenyl groups bonded together in a linear array and are akin to the chlorinated terphenyls. The above authors reported they contained 6 to 10 chlorines with 800 ppm in the Japanese oil and 90 and 100 ppm in the Taiwanese samples. Kamps et al. (1978) earlier identified the presence of PCQs in Yusho oil but no quantitative data were given.

Yamaryo et al. (1979) found the PCQs could be formed from KC-400 by heating for several weeks. At 300 and 350°C, PCQs increased to about 10% of the KC-400 after several weeks.

The presence of PCQs in these rice oils adds yet another dimension to the complexity of the PCB situation, and their role in the toxicity syndromes observed is unknown at this time.

## HUMAN RESIDUES

Although many reports exist in the open literature on PCB residues in aquatic and terrestrial animals, this aspect will not be covered and the reader is referred to reviews by Hutzinger (1974), NAS (1979) and Wasserman et al. (1979).

METABOLISM AND EXCRETION:  
PROBLEMS OF ANALYSIS

When PCBs enter biological systems, the composition of the original PCBs changes, due to metabolism and/or excretion of primarily the lower chlorinated congeners (a chemical compound closely related to another in composition and exerting similar antagonistic effects), so that GLC (gas-liquid chromatography, a technique for separating and identifying compounds) chromatograms no longer match closely standard reference PCBs, such as the commercial Aroclors (Price and Welch, 1972). This complicates the quantitative aspect of analyses.

ACCUMULATION IN  
FATTY TISSUES

PCBs are lipophilic and hence accumulate in fatty tissues.

Human exposure to PCBs was reviewed by Cordle et al. (1978); and they emphasize that in the U.S., minimal exposure occurs through air, water and most food, fresh-water fish being the exception, while significant occupational exposure can occur in industrial workers.

MONITORING OF PCB LEVELS  
IN HUMAN FAT TISSUE

## INCREASING LEVELS

Price and Welch (1972), as part of the National Human Monitoring Program for



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Pesticides sponsored by EPA, reported that of 196 human adipose samples analyzed, 83 (42%) had levels of 1 ppm or more PCB, and only four were negative (based on wet weight). In samples collected in 1973 (1277) and 1974 (1947), 35 and 40%, respectively, of adipose samples (wet weight), had 1 ppm or more of PCBs; and in 1973, 24.5% had no PCBs detected. In 1974, only 9.1% had undetectable levels (Kutz and Strassman, 1976). Most of these residues contained five to seven chlorines per biphenyls. Yobs (1972), from earlier sampling, reported that 235 of 688 samples (34.2%) were negative for PCBs and 32.5% (224) had 1 ppm or more PCBs.

These data indicate that the incidence of PCB residues was increasing; and by 1974, over 90% of the adipose tissues were positive for PCBs.

### HIGHER LEVELS USUALLY INDICATE OCCUPATIONAL OR RELATED EXPOSURES

Occasionally much higher levels are found which usually indicates occupational or related exposures. Biros et al. (1970) estimated 200 and 600 ppm of PCBs in two human adipose samples consisting of at least 14 isomers and congeners ranging from penta- to decachlorobiphenyl. Price and Welch (1972), on a fat basis, reported PCBs in an autopsy case of a 77-year-old man of 115-180 ppm in three adipose samples, 250 ppm in liver, and 125 ppm in kidney. In neither study were the causes of the high levels ascertained.

### WORLD-WIDE LEVELS

NAS (1979) summarized data of PCBs in human adipose tissues and reported the lowest ppm values (fat basis) in New Zealand and Norway (0.9) and highest in

West Germany (FRG) (7.9) with Denmark (5.0), Austria (4.6), East Germany (GDR) (6.4), Japan (4.7), and Israel (3.6) in the middle. The U.S., Canada, and U.K. were 1.2, 1.2, and 1.3 ppm, respectively.

### CANADIAN STUDY: MORE PCBs IN OLDER AND MALE PEOPLE

A recent study (Mes et al., 1982) reported that all 99 adipose samples of Canadians were positive for both Aroclor 1242 and 1260. On a wet weight basis, the mean for 1260 was 0.94 ppm with a range of 0.04-6.80 and for 1242 the mean was 0.31 and range of 0.05-2.30. The authors also found older people to have more PCBs than younger ones and males had more 1260 than females.

### HIGHEST VALUES IN FISHERMEN

These data indicate the world-wide scope of the PCB problem. Generally, the highest values were found in fishermen (IARC, 1978), presumably because they ate more contaminated fish than the average person.

### PCB LEVELS IN BLOOD

Finklea et al. (1972) analyzed blood sera from 616 residents of urban and rural South Carolina and found measurable quantities in 270 (43.8%), ranging from a trace to 29.0 parts per billion (ppb; ng/g).

### ASSOCIATION WITH RACE AND RESIDENCE

They found PCB levels were not related to age or sex of the donor but were associated with race and residence. The rural black donors had the lowest incidence of measurable PCB levels (5 of 107 = 4.7%) rural white had 119 of 192 positive (62.0%)

and urban white had 89 of 166 positive (53.6%) for PCBs. The average of measurable concentrations for these groups were 9.4, 5.2, 5.1 and 4.4 ppb, respectively.

#### LEVELS IN HOSPITALIZED PATIENTS

Hesselberg and Scherr (1974) analyzed venous blood from nine hospitalized patients with severe wasting diseases due to concern with release of PCBs during mobilization of body fat. They were unable to detect PCB in blood of 15 healthy control subjects but found values of 10 to 100 ppb in the patients.

#### DELAYED TESTING OF YUSHO PATIENTS

Unfortunately, levels of PCBs in blood of Yusho patients were only carried out four years after the incident so levels during acute stages of poisoning are not available. Kuratsune et al. (1976) reported PCB plasma levels found in January 1972 for 15 Yusho patients to be 6.3 ppb (range 2-15) about twice that of 82 non-Yusho persons which had 3.0 ppb (range 1-7).

In the more recent Taiwan PCB incident, blood analyses were done from nine months to one year after intoxication. Chen et al. (1980) found whole blood concentrations of 66 Taiwanese patients to have a mean value of 49 ppb with a range of 11 to 720 ppb. The 720 ppb value was considerably higher than others, and this patient had abnormal hepatic and renal functions. Excluding this value, the mean falls to 39 ppb, still considerably higher than normal.

#### LEVELS IN EXPOSED WORKERS

Kuratsune et al. (1976) also reported whole blood PCB levels in 23 workers exposed to Kanechlor 200-600 and found the

mean to be 364 ppb with a range of 60-920 ppb. Two of these workers showed dermal toxicity signs. These latter values undoubtedly were approaching the toxicity threshold.

#### PCB LEVELS IN HUMAN MILK

In human milk from two California cities (Risebrough and Brodine, 1970), the mean PCB level was 0.06 ug/ml (2.0 ppm in fat based on 3% fat). Based on fat content, analysis of 80 samples of human milk from across the U.S. had a mean value of 1.7 ppm with a range of 0.4-10.6 ppm (New York State Health Planning Commission, 1977). Only two samples were negative. From 1969-1974, PCBs in human milk fat averaged close to 1.2 ppm in Ontario residents (Grant et al., 1976). Wickizer et al. (1981) analyzed breast milk samples of 1057 nursing mothers in Michigan from 1977-1978 and found 100% to contain PCBs ranging from a trace to 5.1 ppm (fat basis) with a mean of 1.5 ppm. PCB levels of 2 ppm or more were found in 23.5% of samples and 49.5% of samples had 1-2 ppm.

#### ESTIMATED BODY BURDEN OF PCBs IN INFANTS EXCEEDS RECOMMENDED EXPOSURE LEVELS

Numerous animal studies plus the above reports indicate that PCBs are secreted readily via the mammary glands into the milk. The human public health significance of this phenomenon is unclear at this time. Wickizer et al. (1981) estimated that a child nursing for eight months at the mean PCB level would have an estimated body burden of 0.89 ppm PCB. Risebrough and Brodine (1970) estimated, assuming a daily intake of 150 ml/kg body weight, that breast-fed infants ingested about 9 ug/kg

bw/day of PCBs. Cordle et al. (1978) reports that the maximum allowable ingestion of PCBs recommended for protracted exposure to PCBs is 1 ug/kg bw/day and that the total PCB dose has a 200 mg safety limit. This level of 1 ug/kg/day, is exceeded by the breast-fed infants above, and also in many study subjects in projects reviewed by Cordle et al. (1978).

#### DIFFICULTIES IN DOCUMENTATION OF CHEMICAL EXPOSURE

A recent JAMA article (Rogan, et al. 1983), pointed out the difficulties in documentation of chemical exposure to PCBs. The presence of PCBs and other chemicals in breast milk and the possible effects has been studied since 1978 at Wake Area Health Education Center, East Carolina University School of Medicine, and the Durham Women's Clinic in North Carolina. About 900 breast-feeding children are examined and followed up. In addition to interviews with the mother, review of the child's medical record, physical examination and use of standard development scales, samples of breast milk and serum were collected and analyzed for PCBs on a gas chromatograph with electron-capture detection. In June 1978, a tanker truck discharged hundred of gallons of a used commercial PCB mixture along North Carolina roads. Comparing the levels of PCBs in milk samples of the exposed women with those of other study participants showed no differences. The chromatograms using capillary gas chromatograph analysis showed unusual peaks that indicate the presence of heavily chlorinated PCBs of the kind that were spilled. The authors reported they had not seen illness in the children attributable to PCBs in the milk they received.

## ENZYME INDUCTION

### LIVER EFFECTS FROM PCBs

PCBs produce a number of effects on the liver including:

- 1) Weight increase.
- 2) Fatty liver.
- 3) Porphyria.
- 4) Even cell necrosis (death) at high dose levels (Kimbrough, 1974; Biocca et al., 1976, 1981).

#### METABOLISM OF FOREIGN COMPOUNDS: LIVER FUNCTION

Many organic compounds, falling outside of the category of carbohydrate, protein, fat, steroid or vitamin, are considered foreign to the body. These foreign (xenobiotic) compounds, such as pesticides, drugs, food additives, and including PCBs, are metabolized in the microsomal portions of various tissues, particularly the liver.

#### "MIXED FUNCTION OXIDASE SYSTEM": MFO

The most important reactions involve a general oxidation system referred to as the "mixed function oxidase system" or MFO. This MFO activity usually concentrates in the smooth endoplasmic reticulum (SER) which is particularly abundant in liver cells. When liver cells are ruptured by homogenization, the SER undergoes fragmentation; and when these fragments are separated from other cell components by ultracentrifugation, they are commonly called "microsomes." This microsomal fraction is the source of the xenobiotic (foreign body compound) metabolizing enzymes (MFO).

The MFO requires NADPH as a cofactor and an electron transport system with



cytochrome P-450 as the terminal oxidase. P-450 is so named because in the reduced state it exhibits an absorption band at 450 nm wavelength. More details can be found in the works of Gillette et al. (1969) and Loomis (1978).

#### DETOXIFICATION OR TOXICATION FROM CHEMICAL-INDUCED ACTIVITY OF MFO ENZYMES

The total quantity of MFO enzymes can be increased in man and many animals by prior administration of a variety of chemical substances such as anesthetics, sedatives, analgesics, and insecticides, especially chlorinated hydrocarbons like DDT and dieldrin (Loomis, 1978).

This induction of enzymes represents a mechanism of adaptation by the animal to repeated assaults by xenobiotics and is usually temporary with effects lasting several weeks. This phenomenon of chemical-induced activity of enzyme systems that are responsible for their own degradation, may be protective to the animal (when detoxication is involved) or detrimental (when toxication occurs) (Loomis, 1978).

#### INDUCERS OF LIVER MFO

PCBs are potent inducers of the hepatic microsomal monooxygenases (MFO), responsible for the oxidation of xenobiotics and steroids, in man and experimental animals (Litterst et al., 1972; Alvares et al., 1973).

Most inducers of MFO can be divided into two groups (Echobichon and Comeau, 1974). Prototypic chemicals of these groups are phenobarbital (PB) and 3-methylcholanthrene (3-MC). PB induces cytochrome P-450 and increases the metabolism of a number of substrates while 3-MC in-

duces a distinct subspecies of cytochrome P-450, termed P-448 (or P<sub>1</sub>-450), which differs in spectral qualities and substrate specificity from P-450 (Goldstein, 1979).

Commercial PCBs inhibit enzyme-inducing properties that are termed mixed; i.e. they appear to induce both cytochromes P-450 and P-448 which are classically associated with PB- and 3-MC-induction, respectively (Elcombe et al., 1979). The cytochromes from Aroclor 1254-induced rats are indistinguishable from those induced from PB + 3-MC induced rats (Goldstein, 1979). Aroclor 1254 induces ethylmorphine N-demethylase, preferentially induced by PB, and aryl hydrocarbon hydroxylase (AHH), an enzyme preferentially induced by 3-MC.

#### PCDDs AND PCDFs MORE POWERFUL INDUCERS OF ENZYMES

Complicating the PCB-enzyme induction studies is the fact that certain of the PCDDs and PCDFs, especially those chlorinated in the 2,3,7,8-positions, are potent inducers of AHH and cytochrome P-448, similar to 3-MC, but 30,000 times more powerful (Lucier et al., 1973; Poland and Glover, 1974).

It recently was estimated that some Yusho patients consumed as much as 200 ug of PCDFs/kg body weight (Hoyabuchi et al., 1979). The fact that PCDFs may be 500 times more toxic than the parent compound makes it imperative that dose-related biological effects of the PCDFs be thoroughly understood (Jonsson et al., 1981).

#### INCREASED ENZYMATIC ACTIVITY CAN UPSET NORMAL METABOLISM

The proliferation of the SER (smooth endoplasmic reticulum) in liver cells is an

## POLYCHLORINATED BIPHENYLS (PCBs)

observed effect of exposure to PCBs, PCTs and PCDDs (Norback and Allen, 1972) and is the morphological expression of increased enzymatic activity that can upset normal metabolic pathways in the cell. For example, relatively innocuous substances could be metabolically altered within the liver to produce hepatotoxicity or within the kidney to produce nephrotoxicity due to induced drug-metabolizing activity.

### ENHANCEMENT OF LIVER INJURY

Recknagel and Glende (1973) reported that inducers of cytochrome P-450 (e.g., PB-phenobarbital) can enhance liver injury by carbon tetrachloride. Docks and Krishna (1976) found that the hepatotoxicity of chloroform is augmented by PB pretreatment. Similarly, PB-liver induction enhanced liver injury by bromobenzene (Reid et al., 1971); and the anesthetic halothane was hepatotoxic following PCB-pretreatment (Reynolds and Moslen, 1977).

### BENEFICIAL ENZYME INDUCTION: DETOXICATION

Examples could be cited where enzyme induction could be beneficial by enhancing detoxication of poisons.

Whether the induction of the cytochrome P-450-containing monooxygenase enzyme systems leads to an increase or a decrease in the toxicity of a particular compound is dependent on the toxic properties of the compound in question. If the MFO metabolism of the compound leads to less toxic products, then MFO induction will usually result in a decrease in toxicity. The opposite case would apply when MFO induction yields metabolites more toxic than the parent compound (Doull et al., 1980, p. 68).

### PCBs CAPABLE OF CAUSING REPRODUCTIVE ABNORMALITIES

Induced MFO enzymes also can enhance metabolism of endogenous compounds such as the sex hormones. Aroclor 1262 has an estradiol degrading potential four to five times that of the enzyme inducers p,p'-DDE or technical grade DDT (Edwards, 1971).

PCBs are capable of causing reproductive abnormalities in monkeys related to the changes in the sex hormones and include:

- 1) Irregular and prolonged menstrual cycles.
- 2) Excessive and prolonged hemorrhage during menstruation.
- 3) Reduced conception rate.
- 4) A high incidence of early abortions (Allen et al., 1979).

Orberg (1978) reported that female mice dosed at 0.5 mg/day of 2,5,4'-Trichloro-BP or 2,4,5,2',4',5'-hexachloro BP, for six consecutive days starting on day 1 of pregnancy, have significantly lower frequency of implanted ova than control females which correlated with the significantly increased liver levels of cytochrome P-450.

### ABNORMAL OVARIAN FUNCTION IN YUSHO PATIENTS

Female Yusho patients showed symptoms suggesting abnormal ovarian function with over 60% showing menstrual cycle abnormalities and 55% with abnormal menstrual flow durations (Hirayama, 1976; Kuratsune et al., 1972, 1976).

PCBs also have been shown to reduce the sleeping time induced by hypnotic drugs like PB, pentobarbital and hexobarbital, the time of zoxazolamine-generated paralysis, and the time of action of

other drugs, all attributed to enzyme induction which enhanced metabolism of these chemicals (Wasserman et al., 1979).

### VARIATIONS AMONG PCBs AS ENZYME INDUCERS

Not all PCB isomers (any of two or more chemical compounds having the same elements in the same proportion by weight but differing in physical or chemical properties because of differences in the structure of their molecules) or congeners are potent enzyme inducers or even result in the same type of induction.

The commercial mixtures generally, as stated earlier, are mixed inducers, inducing enzymes characteristic of both PB and 3-MC. Individual PCBs may induce either type. Goldstein et al. (1979) found 2,4,5,2',4',5'-hexachloro-BP resembled PB as an inducer while 3,4,5,3',4',5'-hexachloro-BP resembled 3-MC induction, and neither produced a mixed response at any dose. She found the latter and 3,4,3',4'-tetra-BP to be the only PCB congeners to be 3-MC type inducers. She found striking structural similarities between these two biphenyls and 2,3,7,8-TCDD and TCDF, all potent P-448 inducers, although the PCB isomers are 1000 times less potent than TCDD. Goldstein (1979) reported that most of the hexachlorobiphenyls (2,3,4,2',3',4'; 2,4,5,2',4',5'; and 2,3,5,2',3',5') to be relatively potent PB-type inducers and others (2,4,6,2',4',6' and 2,3,6,2',3',6') to be relatively weak. Most tetrachloro isomers are weak or inactive, with the exception of 2,4,2',4'.

#### PRESENCE AND POSITION OF CHLORINES

For the 3-MC-type inducers, Goldstein (1979) concluded that structural require-

ments appear to be the presence of at least two adjacent chlorines in the lateral positions of the biphenyl and an absence of chlorines in the ortho positions. The addition of one or two ortho chlorines to the biphenyl abolishes 3-MC-type induction. Therefore, 2,3,3',4'-tetra-, 2,3,4,2',3',4'-hexa- and 2,3,4,5,3',4',5'-hepta chloro-BP are inactive 3-MC type inducers. She found that ortho substitution prevents PCBs from assuming a planar configuration characteristic of the toxic PCDDs and PCDFs which are locked into a rigid, relatively planar structure.

The "mixed" inductive effects and much of the toxicity of PCB mixtures are due to the presence of compounds structurally related to the active PCDFs or 3,4,3',4'-tetrachloro-BP.

### IMMUNE EFFECTS

Current procedures for testing the real or potential toxicity of chemicals on animals underestimate the importance of the immune system, especially in chronic studies. As a result, limited data are in the literature on immunosuppressive properties of chemicals.

#### LYMPHOCYTES AND LYMPHOID SYSTEM: BASIS FOR IMMUNE SYSTEM

An animal's immune system is based on small white blood cells called lymphocytes. These cells circulate in the blood, and large populations can be found in tissues of the lymphoid system:

- 1) Bone marrow.
- 2) Thymus.
- 3) Lymph nodes (Fig. 4).
- 4) Spleen.



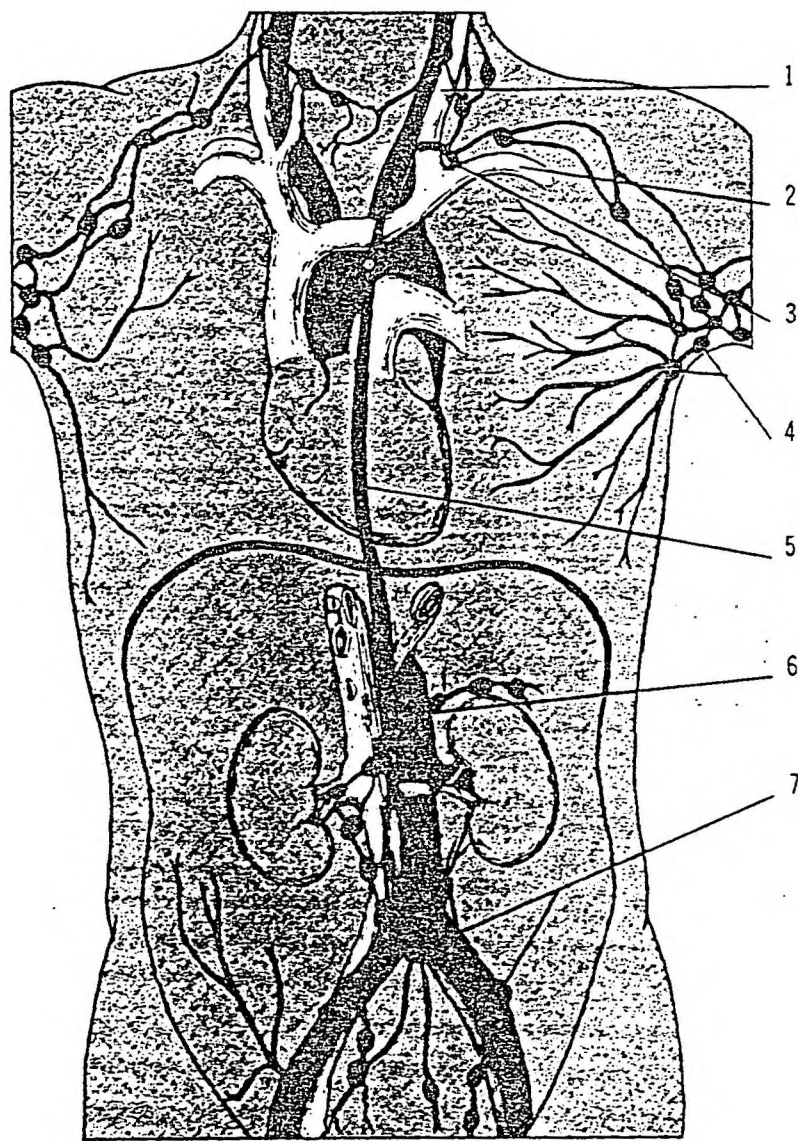


FIG. 4. Lymphatic System and Lymph Nodes

This drawing shows the location of some of the lymph nodes (4 & 7), small oval masses scattered throughout the body. Spaces within the lymph node are occupied by lymphocytes. The lymph nodes supply certain defense cells to the lymph stream and also purify the lymph as it passes through. The lymph is conveyed to and from the nodes by lymph tubes. Phagocytic (scavenger) activity takes place within the node by macrophages and reticular cells.

- |                              |                         |
|------------------------------|-------------------------|
| 1) Internal jugular vein     | 5) Thoracic duct        |
| 2) Left subclavian vein      | 6) Cisterna Chyli       |
| 3) Entrance of thoracic duct | 7) Inguinal lymph nodes |
| 4) Axillary lymph nodes      |                         |

## TRAUMA

- 5) Appendix.
- 6) Tonsils.
- 7) Adenoids.
- 8) Patches of the small intestine.

Lymphoid tissues and organs function as cell production centers and as sites for some immune responses.

### TWO TYPES OF LYMPHOCYTES BASED ON FUNCTION: T-CELLS AND B-CELLS

All lymphocytes originate as stem cells in the bone marrow but are classified into two types based on their functions.

#### T-Cells

Some pass through the thymus (*Fig. 3*) becoming T-cells and specialize mostly as killer T-cells which directly attack their targets (bacteria, fungi, etc.).

#### B-Cells

The other cells, called B-cells, are processed elsewhere, and when stimulated by antigen, become plasma cells and indirectly attack their targets by producing huge numbers of large proteins called "antibodies."

#### Immunoglobulins

These proteins or immunoglobulins (Ig) consist of three main classes called:

- 1) IgG.
- 2) IgA.
- 3) IgM.

IgG is the most abundant antibody produced during a secondary response to antigen (antibody-generator) which combats microbes and their toxins. IgA defends the external surfaces of the body while IgM

is produced early in response to an infection and functions as an agglutinator.

### CELL-MEDIATED IMMUNITY AND HUMORAL IMMUNITY

The T-lymphocytes are responsible for what is termed "cell-mediated immunity," while the plasma cells from B-lymphocytes give rise to "humoral immunity." These two distinct systems of specific immunity are not entirely independent.

In addition, fixed and free macrophages and their precursors (promonocytes in blood) comprise a group of cells which constitute the "mononuclear phagocyte system" (MPS). Macrophages are intimately involved in the initiation and effector phases of both humoral and cell-mediated immune reactions. Further details can be found in the review by Vos (1977).

### CONDITIONS AFFECTING IMMUNE SYSTEM

There is a wide variety of conditions that can affect the immune system, including:

- 1) Glucocorticosteroid hormones.
- 2) Specific nutritional deficiencies.
- 3) Sex hormones.
- 4) Stress factors.
- 5) Infections.
- 6) Irradiation.
- 7) Chemical treatment (Vos, 1977).

### ANIMAL STUDIES ON PCB EFFECTS ON IMMUNITY

#### INCREASED SUSCEPTIBILITY TO HEPATITIS

The first paper on PCB effects on immunity was that of Friend and Trainer (1970) who found PCB-treated mallard

ducklings to have increased susceptibility to duck hepatitis virus. They found two- to four-fold increases in mortality in treated ducklings over that of just virus-stressed birds.

Vos and Beems (1971) found that dermal application of 3 different PCBs (60% chlorine) resulted in toxic effects which included:

- 1) Thymus atrophy.
- 2) Lymphopenia (decrease of proportion of lymphocytes in the blood).
- 3) Spleen and lymph node effects.

#### REDUCTION IN GAMMA GLOBULIN CONTAINING CELLS

In a subsequent study with guinea pigs fed Aroclor 1260 at 10 and 50 ppm, Vos and de Roij (1972) reported no effect on spleen weight and leucocyte count; but the number of  $\gamma$ -globulin containing cells (humoral immune response) in the popliteal lymph nodes was reduced significantly.

Another paper (Vos and van Driel-Grootenhuis, 1972) also involved feeding Aroclor 1260 to guinea pigs at 50 ppm resulting in lymphopenia and depressed secondary antibody response (depressed humoral immunity) to tetanus toxoid. Aspects of these two papers above using Clophen A-60 were deleted because of the known contamination with PCDFs.

#### THYMUS ATROPHY

The extremely toxic 2,3,7,8-TCDF has been shown to cause severe thymus atrophy in chickens, mice, and guinea pigs (Moore et al., 1976); and the thymus is the central lymphoid organ concerned with cell-mediated (T-cell) immune responses (Vos

and Van Genderen, 1973). Additional immune effects can be found in Luster et al. (1979).

#### REDUCTION IN PRIMARY ANTIBODY RESPONSE

Koller and Thigpen (1973) studied the effects of Aroclors 1221, 1242, and 1254 on rabbit response to pseudorabies virus. The number of plaque-forming cells (primary antibody response), was reduced significantly with 1242 and secondary response was depressed significantly in all treatments. Loose et al. (1977) found a 69% decrease in the number of plaque-forming cells per million spleen cells during the primary antibody response to sheep red blood cells (SRBC) in mice fed 1242 for 6 weeks. In contrast to the previous paper, Silkworth and Loose (1981) did not observe the impairment of B-lymphocyte response to mitogen until after 40 weeks of exposure to Aroclor 1016. This was probably due to differences between 1016 and 1242, the latter having considerably more PCB congeners with five or more chlorines. They also found no alterations from control values of body weight or relative spleen or thymus weights but did find significantly greater liver weight due to proliferation of SER.

#### ALTERATION OF CELL AND HUMORAL IMMUNE RESPONSES WITH SUB-TOXIC AMOUNTS OF CHEMICALS

Street and Sharma (1975) studied the alteration of cell and humoral immune responses by 1254 and the insecticides DDT, carbaryl, carbofuran and methyl parathion in rabbits. The rabbits were fed graded doses of clinically sub-toxic amounts of these chemicals for 4 weeks followed by a



challenge with SRBC and Freund's adjuvant antigens and tested for an additional 4 weeks on the same diet. They found decreased numbers of plasma cells in the popliteal lymph nodes, except for carbaryl, reduction in spleen germinal centers and increasing atrophy of the thymus cortex; such responses were dose-dependent which included both cell-mediated and selected humoral immune response reductions. The paper by Loose et al. (1981) indicated that no alteration occurred in *in vitro* phagocyte activity or capacity or microbiocidal activity of macrophages from mice fed 1242 at 5 and 100 ppm in their diets. Weirda et al. (1981) found that 1254 could preferentially inhibit the generation of antibody-producing cells in mice.

#### PCBs AND SELECTIVE TOXICITY ON DIFFERENT PORTIONS OF IMMUNE SYSTEM

The above papers suggest that PCBs can express selective toxicity on different portions of the immune system and that the target site for the resultant reduction in humoral (antibody-mediated) immunity is a mechanism and/or cell type distinct from components of cell-mediated immunity (Silkworth and Loose, 1981). The paper of Vos and Van Driel-Grootenhuis (1972) and Street and Sharma (1975) involving thymus effects by PCBs, indicate toxic effects also on cell-mediated immunity which, all in all, indicate species differences in the susceptibility to PCB-induced immunotoxicity. Interestingly, Battson et al. (1981) found the very persistent 2,4,5,2',4',5'-hexachlorobiphenyl given orally to mice to have very marginal effects on the immune system. The other results cited above may, at least partly, mirror effects induced by contaminants.

#### MECHANISMS OF IMMUNOSUPPRESSION UNKNOWN

According to Luster et al. (1978), there are no data to show that PCBs cause their immunosuppressive effects directly and that they may alter physiological or pathological conditions which indirectly affect the immune system. Luster et al. (1979) claimed that the mechanisms of immunosuppression for environmental chemicals, including PCBs, PCDDs or PCDFs, are presently unknown.

#### EFFECTS OF MONKEY MOTHERS FED PCB DIET PASSED TO OFFSPRING

Allen et al. (1980) in rhesus monkeys, non-human primates, fed 2.5 or 5.0 ppm of Aroclor 1248 in their diets for 18 months and after being on PCB-free feed for about 1 year, were bred. After birth, their offspring were nursed for 4 months and then weaned. Two of seven offspring from mothers fed 2.5 ppm PCB and two of four from mothers fed 5.0 ppm PCB died after weaning. Histology of tissues from these four infants showed hypocellularity of the cortical and medullary zones of the thymus, and the spleens also were small with very few lymph nodules. The lymph nodes were hypocellular and devoid of germinal centers, and the bone marrow was hypoactive with most cells present being of the mature variety. These infants had essentially no thymus and only rudimentary lymphoid tissues and had many other signs of PCB intoxication even through their mothers were not exposed to PCBs for approximately 2 years. Their deaths were attributed to immunologic deficiency. Even though the mothers appeared healthy, these female primates were capable of carrying sufficiently high PCB body burdens,

after exposure was terminated, to produce severe ill effects, including death, in their offspring through their contaminated milk.

### LIMITED DATA ON IMMUNE EFFECTS IN YUSHO PATIENTS

Surprisingly, there are essentially no data on immune effects of PCBs in Yusho patients. Ueda (1976) reported data on Yusho victims suggesting a reduced resistance to respiratory infection. This was based on findings in a few cases of markedly reduced levels of IgA. He reported that serum IgA and IgM levels were decreased and IgG levels increased in 1970 (2 years post incident) but generally were in the normal range by 1972. Those patients with severe dermatological symptoms had significantly lower levels of IgM.

### PCBs AFFECT THYROID FUNCTION IN ANIMALS

There is little question that the PCBs affect the thyroid function of animals (Barsans, 1981), leading to decreased serum thyroxine levels. Such effects can indirectly have a deleterious affect on the immune system (Vos, 1977).

## LUNG EFFECTS

In both clinical and epidemiological studies, the respiratory system has been suspected to be one of the target sites for PCB poisoning in man.

### RESPIRATORY FINDINGS IN YUSHO PATIENTS

Hirayama (1976) reported PCBs in the lung and sputum of Yusho patients, and postulated that the many cases of chronic

bronchitis seen may be due to a PCB effect on some defense mechanism.

### CHRONIC BRONCHITIS

Chronic bronchitis in Yusho victims was indicated by respiratory symptoms of profuse expectoration, cough and bronchographic findings (Kuratsune et al., 1976).

Shigematsu et al. (1978) conducted clinical, laboratory, and pathological studies in 401 Yusho patients to assess respiratory effects. They found the incidence and severity of respiratory symptoms to correlate well with PCB concentrations in the blood and sputa.

### IMPAIRMENT IN LUNG VITAL CAPACITY IN WORKERS EXPOSED TO PCBs

Warshaw et al. (1979) reported an increased prevalence in restrictive impairment in lung vital capacity in workers exposed to PCBs. They found 34 of 243 workers in capacitor manufacturing with reduced spirometric measurements.

### ANIMAL STUDIES SHOWING ACCUMULATION OF PCBs IN BRONCHI, LARYNX AND TRACHEA

Brandt (1975a) found that <sup>14</sup>C-labeled 2,4,5,2',4',5'-hexachloro-BP accumulated and was retained in the bronchial mucosa and in the mucosa of the larynx and trachea in mice. Berlin et al. (1975) found a similar distribution for 2,4,5,2',5'-pentachloro-BP. This site of accumulation of PCBs was considered unique by Brandt since previous studies (Brandt, 1975b) indicated that PCBs were not taken up by the bronchi but were evenly distributed

throughout the lung parenchyma (functional element of an organ) as shown with both 2,3,4,6,2',4'- and 2,4,6,3',4',5'- hexachloro-BPs.

Brandt et al. (1976), using  $^{14}\text{C}$ -labeled PCBs, showed that PCBs with chlorines in positions 2,5,4' and hydrogens in 3,6,3',6' are accumulated in the bronchial mucosa as shown using 2,4,2',5'-tetrachloro-BP. Brandt (1977) reported that both  $^{14}\text{C}$ -labeled 2,5,4'-tri- and 2,4,5,2',4',5'-hexachloro-BP showed a remarkably strong and persistent accumulation of radioactivity in the entire bronchial lining of mice following i.v. (intravenous) or i.p. (intra-peritoneal) injection.

#### COMPOUNDS PASSED THROUGH PLACENTA BARRIER

He found also that both compounds passed through the placental barrier of pregnant mice and were concentrated in a similar manner in the bronchi of the fetal lung.

#### PCBs WITH SPECIFIC AFFINITY FOR LUNG PARENCHYMA

In a recent paper, Brandt et al. (1981) reported that a number of pentachloro-BP with chlorines in the 2,3,6-positions possess a specific affinity for the lung parenchyma. This is in contrast to his previous work which showed that a 2,4,5-substitution pattern is characteristic for all the bronchial-seeking compounds. This recent work was done with 2,3,6,2',3'-, 2,3,6,3',4'-, 2,3,6,2',5'-, and 2,4,5,3',5'-pentachloro-BPs. The first three showed a specific accumulation in the lung parenchyma whereas the last did not accumulate in lung tissue. Bergman et al. (1979) found that, of 17 PCB congeners studied, 2,5,4'-tri-, 2,4,2',5'-

tetra-, and 2,4,5,2',5'-pentachloro-BPs occurred in the lung tissues of mice treated i.v. with these PCBs as methylsulfonyl PCB metabolites. This suggested that these metabolites are responsible for the specific bronchial accumulation found earlier (Brandt 1977). They also found the lung/liver concentration ratio to increase with time.

The above findings, that certain defined PCBs accumulate in the lung parenchyma whereas others accumulate in the bronchial mucosa, may lead researchers to the mechanism behind the respiratory involvement of PCB poisoning.

#### REPRODUCTION AND ENDOCRINE EFFECTS

Various studies have shown the limitation of rodents as animal models in investigations of PCB toxicity effects. For example, Allen et al. (1976) found that rats on diets containing 100 ppm of Aroclor 1248, 1254 or 1262 were able to survive for 1 year without showing signs of illness. This is in marked contrast to the monkey data below.

#### TOXICOLOGICAL SIGNS IN MONKEYS SIMILAR TO THOSE IN MAN

Allen et al. (1979) reported on studies of PCB effects on reproduction in non-human primates, rhesus monkeys, an animal model whose toxicological signs produced by PCBs are similar to those produced in humans (Allen and Norback, 1976).

#### ALTERATIONS IN MENSTRUAL CYCLE

Adult female monkeys were fed 2.5 or 5.0 ppm Aroclor 1248 in their diets and



within 4 months had markedly altered menstrual cycles (*Figs. 5 & 6*). They found menses to be 5-7 days longer than control animals with an accompanying increase in menstrual bleeding. They observed also a flattening and prolongation of the serum progesterone peak during the menstrual cycle.

#### REPRODUCTIVE EFFECTS

These females were bred after 7 months on this diet (having consumed 105-210 mg PCB) with all control and all animals on the 2.5 ppm diet and 6 of 8 females on the 5.0 ppm diet conceiving. The remaining two were bred on five separate occasions without conceiving. However, 3 of the 8 females on the 2.5 ppm diet and 4 of 8 on the 5.0 ppm diet experienced early abortions or resorptions and 1 female on the 5.0 ppm diet delivered a stillborn infant. Only 1 female at the 5.0 ppm diet while 5 females on the 2.5 ppm diet were able to carry their infants to term.

#### CHANGES IN SEX HORMONES

Allen et al. (1979) related the above problems to changes in the sex hormones. They found that those monkeys showing no alterations in serum estradiol and progesterone experienced none of these reproductive problems whereas in those animals with the most dramatic hormone changes, the reproductive alterations were most severe even leading to anovulatory (absence of discharge of ovum) states in some cases.

These hormone changes may be due to the degradation of hormones resulting from increased levels of induced liver MFO enzymes.

#### Allowable PCB in Food for Human Consumption

It is noteworthy that PCB levels up to 3.0 ppm presently are permitted in food intended for human consumption.

#### TRANSPLACENTAL MIGRATION AND MILK INGESTION OF PCBs

Allen and Norback (1976) reported that all infants born to Aroclor 1248-exposed female monkeys contained PCBs in their tissues at birth due to transplacental migration.

These infants were exposed continuously to PCBs by ingestion of milk from their lactating mothers and developed skin lesions, and 50% died from PCB intoxication within 4 months.

#### EFFECTS OF LOW LEVEL DIET

Barsotti and Allen (1975) and Barsotti et al. (1976) found that rhesus monkeys which were fed low levels of Aroclor 1248 developed, besides chloracne:

- 1) Menstrual irregularities.
- 2) Increased excretion of urinary total ketosteroids.
- 3) Reduced conception rates.
- 4) Increased incidence of abortions.
- 5) Birth of small infants.

#### STUDY OF YUSHO PATIENTS

##### SUGGESTED ABNORMAL OYARIAN FUNCTION

Hirayama (1976) summarized results on female Yusho patients whose symptoms suggested abnormal ovarian function. He reported that:

- 1) Over 60% of these patients showed abnormalities in their menstrual cycle.

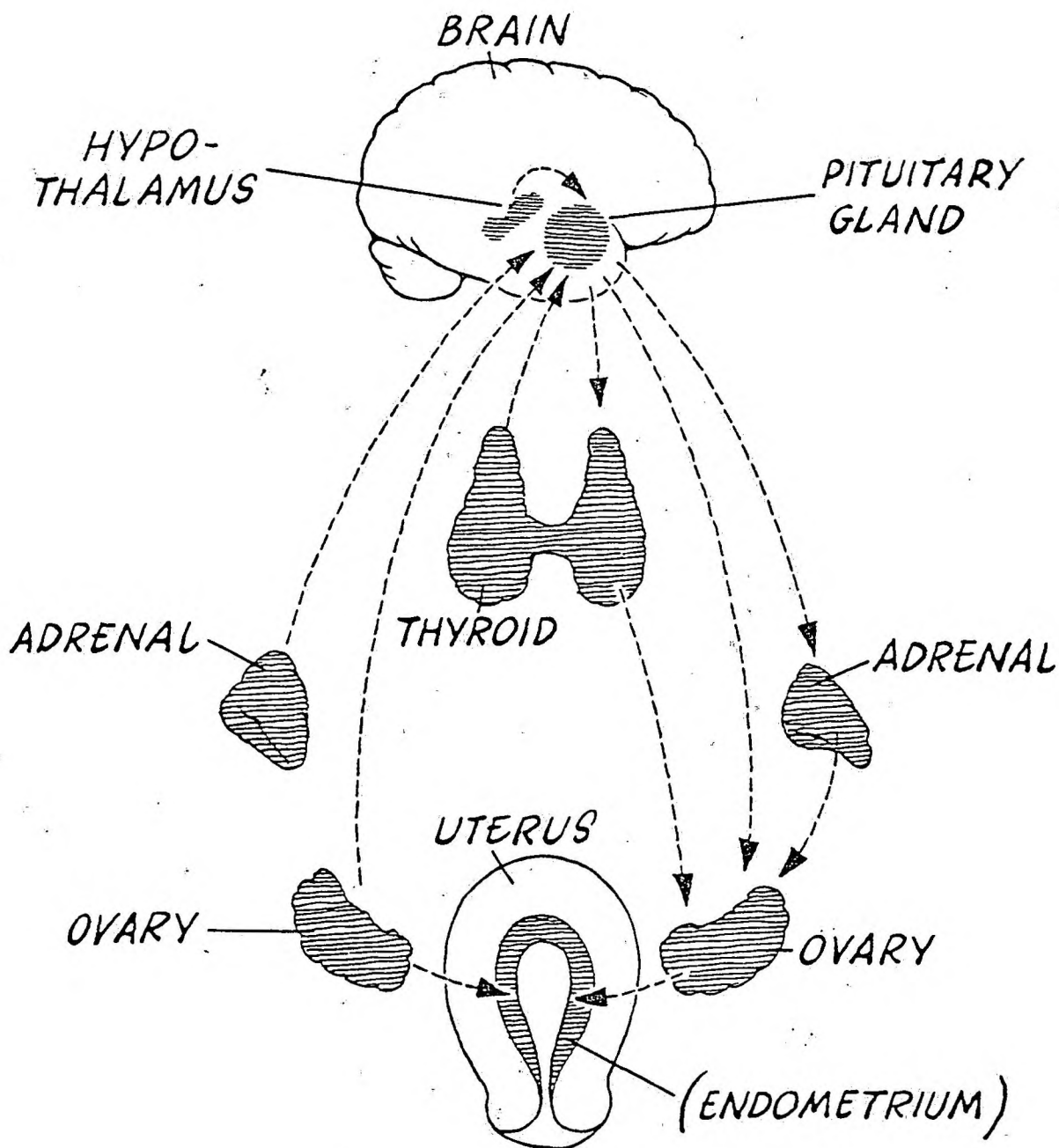


FIG. 5. Diagrammatic Sketch Showing Functional Interrelationships of Endocrine Glands Involved in Menstrual Cycle

Normal menstrual function is dependent on the integrated action not only of the ovaries and uterus, but also of the thyroid gland, pituitary gland, hypothalamus and adrenal glands. Upon stimulation by the hypothalamus, the pituitary gland produces the gonadotrophic hormone. The gonadotrophic hormone is composed of two components known as the follicle-stimulating hormone (Prolan A) and the

- 2) About 55% had abnormal durations of menstrual flow.
- 3) 85% showed an abnormal pattern in basal body temperature.

This latter point indicated corpus luteum (Figs. 5 & 6) insufficiency, retarded follicle maturation or no ovular cycle. There was also a low output of urinary estrogen and pregnanediol, especially in the luteal phase. He concluded that these abnormalities may have resulted from primary ovarian disorders, secondary suppression by other glands, or some abnormal function of the target organs.

It should be considered that these problems may be due, at least partially, to abnormal degradation of sex hormones by PCB-induced MFO enzymes in the liver.

## NEUROLOGICAL AND BEHAVIORAL EFFECTS

The area of neurological and behavioral effects is a relatively poorly researched area regarding PCB effects.

### FINDINGS IN YUSHO INCIDENT

In the summer of 1970, more than 2 years after the Yusho incident, Kuratsune et al. (1972) found that about 50% of 159 patients examined showed clinical improvement; the remaining half did not and more than 10% showed worsening symptoms.

### PATIENTS' COMPLAINTS

They indicated that even many of those who appeared to be clinically improving had several serious complaints, all pointing to neurologic disorders, such as:

- 1) Persistent headache.
- 2) General fatigue.
- 3) Feelings of weakness and numbness in limbs.

### PERIPHERAL NEUROPATHY SELECTIVE FOR SENSORY NERVES

Murai and Kuroiwa (1971) found neurological symptoms of Yusho patients also comprised headaches, numbness, hypoesthesia, and neuralgia. They found a peripheral neuropathy selective for sensory nerves in studies on nerve conduction velocity. This sensory neuropathy was documented in 10 out of 12 patients with known PCB poisoning.

### POSSIBILITY OF FUTURE WIDER NEUROLOGICAL EFFECTS

Hirayama (1976) carried out neurological and electrophysiological examinations to elucidate the neurological disorders reported by Kuratsune et al. (1972). He found no symptoms or signs which indicated involvement of the cerebellum, spinal cord or cranial nerves. He did report, how-

FIG. 5. Diagrammatic Sketch Showing Functional Interrelationships of Endocrine Glands Involved in Menstrual Cycle—continued (see page 2: 90)

luteinizing hormone (Prolan B). Each of these two substances appears at its own specific time in the menstrual cycle, and each produces a specific effect on the ovary for a specific period of time. The follicle stimulating hormone appears at the beginning of a cycle, and its function is to stimulate the ovary to mobilize and prepare one of its ova for fertilization.



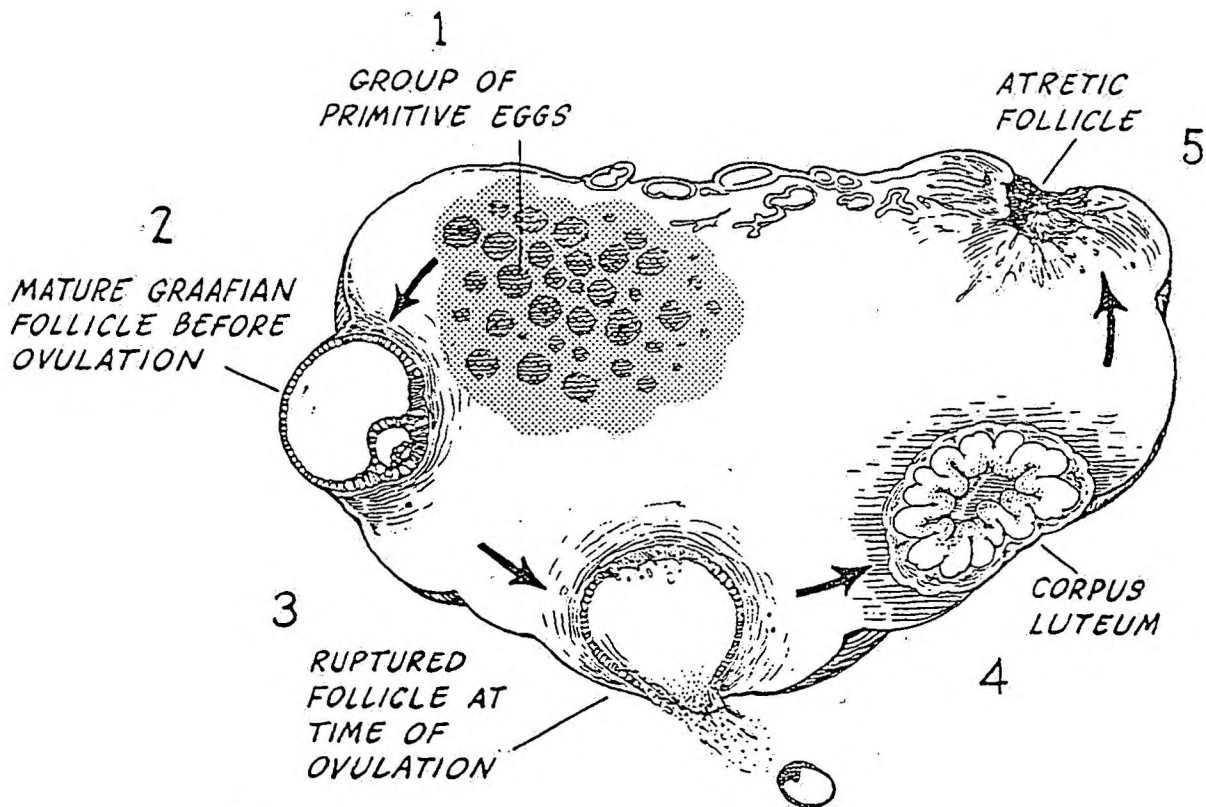


FIG. 6. Diagrammatic Sketch Showing Structures Associated with Menstrual Cycle

The increasing output of follicle stimulating hormone causes the ovum to move from the deeper central portion of the ovary to the outer margin until it approaches the surface of the ovary. As the ovum is changing its location over a period of 12 to 14 days, other changes take place in the follicle, the structure surrounding the egg. Cells become rearranged and increased in number and size, as well as activity, forming the graafian follicle, which contains the egg and estrogen-producing cells and a clear fluid. Estrogen enters the blood vessels, uterine wall musculature and especially the lining of the uterus cavity (the endometrium) and its gland. The principal effect of these stimulatory changes is to increase the amount of fresh blood to the endometrium and to change other substances and enzymes necessary for transport of spermatozoa and sustenance of the fertilized egg. The developing graafian follicle gradually increases through the first three fourths of the cycle.

Ovulation occurs when the follicle ruptures and releases the egg and fluid around it. The chemical changes associated with ovulation cause certain cells in the pituitary gland to produce a second gonadotrophic hormone substance, known as the luteinizing hormone or prolactin B. This chemical agent acts on a group of cells which have grown into the ruptured follicle and have formed a hormone-producing gland called the corpus luteum. The corpus luteum produces a second female hormone, progesterone, which is essential to the development of a fertilized

ever, significant involvement of the peripheral nerves, almost exclusively sensory nerves. He concluded that present findings (up to 1975?) may have revealed only the early manifestations of wider neurological effects.

### BEHAVIORAL DEFICITS IN MONKEY OFFSPRING

Indirectly related to neurological effects, are the findings by Bowman et al. (1978) that monkeys have behavioral deficits when weaned from mothers fed 2.5 ppm PCBs in their diets. Only 3 of such 5 infant monkeys born to these mothers survived past weaning at 4 months of age. Behavioral tests with these 3 survivors plus 4 normal controls revealed hyperlocomotor (excessive movement from place to place) activity at 6 and 12 months which correlated with peak PCB body burdens. The monkey with the lowest body burden at 4 months of age (21 ppm, their point estimate for a zero-effect level) still exhibited some behavioral defects persisting through the final testing at 24 months of age.

### "SPINNING SYNDROME" IN MICE

Chou et al. (1979) reported that a striking motor dysfunction, "spinning syndrome," developed with a high frequency in weanling mice whose mothers received

32 mg/kg/day of the toxic 3,4,3',4'-tetrachloro-BP during gestation days 10 through 16. Induction of this permanent syndrome in mice strongly indicates that this PCB congener is not only fetotoxic and teratogenic but also neurotoxic for the developing central nervous system. This PCB isomer resembles the highly toxic 2,3,7,8-TCDF. The roles that PCDFs and PCQs play in these effects are unknown at this time.

The above data indicate the need for more extensive studies on neurological effects, especially with monkeys, and also continued follow-up of the human victims of PCB poisoning in Japan and Taiwan.

### LIVER EFFECTS

The liver is one of the most susceptible organs to the effects of both acute and chronic doses of PCBs, both commercial mixtures and pure isomers.

### LIVER ENLARGEMENT

A number of authors has described liver enlargement as a consequence of PCB exposure which has been considered due primarily to hypertrophy (overgrowth) of the smooth endoplasmic reticulum (SER) of the liver cells (Allen et al., 1973; Kimbrough, 1974; Nishizumi, 1970; Vos and Beems, 1971).

FIG. 6. Diagrammatic Sketch Showing Structures Associated with Menstrual Cycle  
—continued (see page 2: 92)

egg. If no pregnancy occurs, the corpus luteum degenerates because of declining production of luteinizing hormone by the pituitary and a rapid decrease of progesterone. With a lack of essential supporting chemicals, the endometrium degenerates. A shedding off and expulsion of about 80% of this lining, together with a varying amount of blood, is expressed externally as the menstrual flow.

## MFO ENZYME INDUCTION

This increase in the SER of liver cells is accompanied by an induction of microsomal MFO (see section on Enzyme Induction, p. 79) and is more marked with the more highly chlorinated PCBs and relatively low with Aroclors 1221 and 1016 (Echobichon and Comeau, 1974). This has also been demonstrated with single pure PCBs where a greater degree of enzyme induction occurs with the higher chlorinated isomers (Johnstone et al., 1974).

## HEPATOMEGALY IN ALL SPECIES AT BELOW LETHAL LEVELS

McConnell and Moore (1979) concluded that pathology of the liver by PCBs is interesting because it is so conspicuous in some species (mice, rats, rabbits and chickens) and so minimal in others (guinea pigs and monkeys). However, they report hepatomegaly (both absolute and percent of body weight) to be observed consistently in all species and at exposures considerably below the lethal dose.

Koller and Zinkel (1973) found that the hallmark of acute toxicity in rabbits was hepatocellular necrosis with hemorrhage.

## VARYING TOXICITIES OF PCB ISOMERS

Biocca et al. (1981) studied the toxicity of four symmetrical hexachloro-BPs in young female mice dosed at levels from 0.3 to 300 ppm in the diet for 28 days. These PCB isomers were chlorinated in the 3,4,5 or 2,4,5 or 2,3,6 or 2,4,6 positions. The 3,4,5,3',4',5'-hexachloro-BP was by far the most toxic isomer causing mortality, body and organ weight effects at all levels and was the only isomer which produced excess porphyrin accumulation. The liver effects it caused were enlargement, accentu-

ated lobular markings, fatty infiltration, hepatocellular swelling and necrosis. The 2,4,6 and 2,4,5 isomers caused the same lesions but to a lesser degree, and the 2,3,6 isomer was the least toxic. Biocca et al. (1976) noted that the effects of the 3,4,5 isomer mimic those caused by the PCDFs.

## PORPHYRIA

Goldstein et al. (1974) fed female rats 100 ppm Aroclor 1254 in the diet for up to 13 months. Hepatic porphyria (excess formation of porphyrin in the liver) occurred in all rats fed for at least 7 months and was characterized by delayed onset, excretion of large amounts of 7- and 8-carboxyporphyrins in the urine and accumulation of uroporphyrins in the liver. Porphyria is a disturbance in porphyrin metabolism characterized by a marked increase in formation and excretion of porphyrins which resembles human porphyria cutanea tarda. This syndrome is characterized biochemically by an increase in the activity of the mitochondrial enzyme  $\alpha$ -aminolevulinic acid synthetase (ALA), which is the first and rate-limiting enzyme in the heme biosynthetic pathway (Woods, 1973). Goldstein et al. (1974) found that no induction of ALA synthetase could be demonstrated prior to the onset of porphyria in rats. Goldstein et al. (1976), using the same symmetrical hexachloro-BPs as Biocca et al. (1981) cited above plus the 2,3,4 isomer, found all hexachloro-BPs to cause uroporphyrin accumulation and increased ALA synthetase activity in chicks but only the 3,4,5 and 2,3,4 and 2,3,5-hexachloro-BPs produced gross accumulations of hepatic porphyrins. It is notable that all three of the above hexachloro-BPs with potent effects had chlorines in both the meta- and para-positions. Goldstein et al. (1976)



found the 3,4,5,3',4',5'-isomer to accumulate the most in fat and liver of chicks and was lethal. Interestingly, 2,3,7,8-TCDF did not cause these effects in chicks. Their results indicate that TCDF plays no significant role in the production of porphyria by PCB mixtures.

#### PORPHYRIAS ACCOMPANIED BY CHRONIC LIVER DAMAGE

Strik (1979) stated that chronic hepatic porphyrias were always accompanied by chronic liver damage and existed in clinically latent and manifest stages. He said these stages could be both recognized and differentiated on the basis of the characteristic porphyrin excretion in urine, fluorescence of porphyrins in liver preparations and the accumulation of uro- and heptacarboxylic porphyrin in the liver. He could characterize the chronic stages into types A, B, and C according to the type of porphyrin in the liver, the extent of porphyrinuria, and the relative distribution of uroporphyrin, coproporphyrin and porphyrins with 5 to 7 carboxylic groups in the urine. Type A, the mildest form, marked the start of the progression. Strik (1979) reported on a study that indicated that a significant difference was not found in liver function tests, urinary total porphyrins and porphyrin pattern between 16 Yusho patients and Japanese control subjects. This, however, was done several years after the incident.

#### HUMAN PORPHYRIA POSSIBLE FROM HIGH-LEVEL PCB CONTAMINATION OF FOOD

The dietary level of Aroclor 1254 used by Goldstein et al. (1974) to produce porphyria in female rats (100 ppm) is at least 30 times higher than the 0.2 to 3 ppm tolerances set by FDA for PCBs in foods in

the U.S. (FDA, 1977). They stated that it is unlikely that present levels of PCBs in the environment of the U.S. today will result in porphyria in humans. However, one should remember that accidental poisonings, such as the Yusho incident in Japan and the more recent episode in Taiwan, do occur and there have been several incidents of other food materials being contaminated with PCBs (Heritage, 1978).

#### BIOLOGICAL DATA RELEVANT TO HUMANS

Data from many animal studies may give clues to similar effects in humans. The following are discussed in this section:

- 1) Metabolism.
- 2) Tissue distribution, accumulation and depletion of PCBs.
- 3) Carcinogenicity.
- 4) Teratogenicity.
- 5) Effects on digestive system.
- 6) Vitamin effects.

#### METABOLISM

Many halogenated hydrocarbons are excreted slowly from humans and animals and thus may persist in the tissues for years. It has been assumed that these chemicals, including PCBs, are inextricably deposited in fatty (adipose) tissues based on evidence of limited biotransformation with minimal urinary excretion and high lipid (fat) solubility.

#### QUALITATIVE AND QUANTITATIVE DIFFERENCES IN BIOLOGICAL EFFECTS

Considerable amounts of data are now extant which indicate that there are very important qualitative as well as quantita-

tive differences in the biological effects of different PCB congeners (chemical compounds closely related to another in composition).

Hansen (1979) pointed out that disappearances of PCB residues are dependent on absorption, distribution, metabolism and excretion which vary from PCB congener to congener and from species to species.

#### CHLORINATION OF BIPHENYL MOLECULE MARKEDLY AFFECTS METABOLISM AND DISPOSITION

The unsubstituted biphenyl molecule is readily metabolized by the hepatic MFO. The two phenyl rings have a directing effect on the enzymatic attack on the biphenyl molecule. The major metabolite of biphenyl is the 4-hydroxy derivative with 2-hydroxy biphenyl as a secondary metabolite (Billings and McMahon, 1978). These two metabolites may be formed by different enzymes since the 4-hydroxy biphenyl is induced by pretreatment with PB while 3-MC is a better inducer of 2-hydroxy biphenyl formation.

Chlorination of biphenyl has marked effects on its metabolism and disposition. Block and Cornish (1959) found that addition of a single chlorine directs the hydroxylation to the unchlorinated ring. With the addition of two or more chlorine atoms on biphenyl, the position of chlorination becomes of critical importance in the rate of metabolism and thus of the biological half-life of the PCB (Matthews and Kato, 1979).

#### "NIH-SHIFT" OF CHLORINE ATOM AND FORMATION OF ARENE OXIDE INTERMEDIATE

In the rat, the initial half-life of 4,4'-dichloro-BP is about 1 day, twice as long

as that of 4-chloro-BP (Matthews and Anderson, 1975a). The major metabolite of 4,4'-dichloro-BP excreted by the rat is 4-hydroxy-3,4'-dichlorobiphenyl indicating the famous "NIH-shift" of a chlorine atom; this implies formation of an arene oxide intermediate between chlorinated and non-chlorinated carbon atoms (Hess et al., 1977).

#### SPECIES DIFFERENCES IN METABOLISM

There are species differences in metabolism of the para-chlorinated 4,4'-dichloro-BP. The rat and dog metabolize and excrete it to indicate a half-life of 1 day. The monkey metabolizes and excretes it much more slowly, and the initial half-life in the monkey is 2-3 weeks (Matthews and Kato, 1979). Therefore, this PCB can bioaccumulate in the monkey but not in the rat and dog.

#### POSITION OF CHLORINATION INHIBITS METABOLISM, AFFECTING HALF-LIFE

The position of chlorination can confer metabolic hindrance to varying degrees. For example, the initial half-life of 2,4,5,2',5'-pentachloro-BP in rats is twice as long as 4,4'-dichloro-BP (Matthews and Anderson, 1975b). Adding an additional chlorine in the 4'-position to form 2,4,5,2',4',5'-hexachloro-BP inhibits the metabolism of this PCB so greatly that its half-life exceeds the lifetime of the animal (Matthews and Anderson, 1975a). Jensen and Sundstrom (1974) found this hexachloro-BP to be in the highest concentration of any PCB found in adipose tissue samples from Sweden.

#### METABOLIC STUDIES

A substantial number of metabolic studies of commercial mixtures, individual

## POLYCHLORINATED BIPHENYLS (PCBs)

PCB congeners and metabolites have been reported and comprehensive reviews have been published (Hutzinger et al., 1974; Sundstrom et al., 1976; NIOSH, 1977; IARC, 1978).

### EASE OF METABOLISM DECREASES WITH INCREASING CHLORINE CONTENT

In PCB-treated animals, GLC peaks with retention times corresponding to di-, tri- and tetrachlorobiphenyls are diminished or absent in tissue extracts which is indicative of metabolism of these components in commercial mixtures. This was evident in studies with mice, rats, birds and cows (Hutzinger et al., 1974). One can conclude that the ease of metabolism decreases with increasing chlorine content. Available data indicate also that chlorine positioning on the biphenyl rings influence metabolic behavior.

The reviews, cited above, indicate that ease of metabolism decreases in the order mammals > birds > fish, and that PCBs are metabolized to mono- and dihydroxylated metabolites dependent on extent and

position of chlorine substitution. They concluded that fecal extracts usually contain the free phenol while urinary metabolites are both free and conjugated.

Hutzinger et al. (1972) studied the metabolic behavior of four pure PCBs in pigeons, rats, and brook trout. Their results showed that rats and pigeons could convert 4-mono, 4,4'-di- and 2,5,2',5'-tetrachloro-BPs into monohydroxylated derivatives, but no hydroxyproducts were found in excreta of brook trout. No hydroxylated products of 2,4,5,2',4',5'-HCB were detected in excreta of rats, pigeons or brook trout. Jensen and Sundstrom (1974b) did report this HCB to be only slowly hydroxylated in mice.

### VARYING PERSISTENCE OF PCBs IN ENVIRONMENT

Ballschmiter et al. (1978) reported the extreme persistence of several penta-, hexa- and octachloro BPs while certain others do disappear from the global environment. These data are presented in Table 10.

Table 10  
SOME EXTREMELY PERSISTENT AND LESS PERSISTENT  
PCB CONGENERS<sup>a</sup>

| Extremely Persistent             | Less Persistent             |
|----------------------------------|-----------------------------|
| 2,4,5,2',4'-pentachloro          | 2,3,4,2',3'-pentachloro     |
| 2,3,4,2',4'-pentachloro          | 2,3,4,5,2',3'-hexachloro    |
| 2,3,4,5,2,4'-hexachloro          | 2,3,4,6,2',5'-hexachloro    |
| 2,3,4,2',3',5'-hexachloro        | 2,3,4,5,6,2',3'-heptachloro |
| 2,3,4,5,6,2',3',5'-octachloro    |                             |
| 2,3,4,5,6,2',3',4',5'-octachloro |                             |
| 2,3,4,5,6,2',3',4'-octachloro    |                             |
| 2,3,4,5,2',4',5'-octachloro      |                             |

<sup>a</sup> Penta- and hexachloro-BP are present mainly in Arocloro 1254 and Clophen A-50 while hepta- and octachloro-BP are present mainly in Aroclor 1260 and Clophen A-60.



## METABOLIZATION TO SULFUR DERIVATIVES

The PCBs, although chemically stable, are known to be metabolized by various animal species to hydroxylated derivatives (reviewed by Sundstrom et al., 1976) and are now known to be metabolized to sulfur derivatives as well. Mio et al. (1976) identified two methylthio and two methylsulfonyl derivatives from excreta of mice treated with 2,5,2',5'-tetrachloro-BP. Jensen and Jansson (1976) found large numbers of methylsulfonyl derivatives from tri-, tetra-, penta-, and hexachloro-BPs in blubber of seals from the Baltic Sea. Bergman and Wachtmeister (1978) also reported unpublished data of finding methylsulfonyl metabolites in fat samples from a number of other species as well. These data indicate that these transformations represent a general metabolic pathway of most, if not all, PCBs (Bergman et al., 1979).

Jensen et al. (1979) found that, in contrast to phenolic metabolites of PCBs which are rapidly excreted from the body, the methyl sulfones are accumulated.

## FORMATION OF ARENE OXIDE INTERMEDIATES: TOXIC AND CARCINOGENIC PROPERTIES OF PCBs

The PCB problem may be further complicated by metabolism since those PCB congeners most easily metabolized and excreted are those most likely to form arene oxide intermediates (Matthews et al., 1978).

Jerina and Daly (1974) found that metabolic formation of arene oxides explains many toxic and/or carcinogenic properties of aromatic hydrocarbons. They reported that arene oxides, in which an aromatic double bond has undergone epoxidation, in addition to isomerizing to phenols, react readily with a variety of nu-

cleophiles, including such macromolecules as DNA, RNA and protein. The importance of two adjacent unsubstituted carbon atoms to the metabolism of PCBs was emphasized by Matthews et al. (1978) since formation of arene oxides was greatly facilitated by this requirement. Morales and Matthews (1978) found that exposure of mice to 2,3,6,2',3',6'-hexachloro-BP led to arene oxide formation which became covalently bound to nucleic acids and protein of a number of mouse tissues. The toxicologic significance of such covalent binding remains to be determined.

One can conclude, however, that the production of less chlorinated PCB formulations (Aroclor 1016) and the decline in production of more highly chlorinated PCBs (Aroclor 1242) may have helped to alleviate some long-term residue problems only to intensify other problems.

## TISSUE DISTRIBUTION, ACCUMULATION AND DEPLETION OF PCBs

## ACCUMULATION

Since PCBs are extremely water-insoluble, and therefore lipophilic, it has been well-established that they accumulate in the fatty tissues of animals.

After an oral dose of 500 mg/kg of Aroclor 1254 to rats, Grant et al. (1971) found concentrations of PCBs in fat, liver and brain of 996, 116, and 40 mg/kg (ppm), respectively, 4 days after dosing. With the same PCB, similar high fat concentrations were found in rats after administration orally (Curley et al., 1971), in cows (Platonow and Chen, 1973), and in boars (Platonow et al., 1972).

## POLYCHLORINATED BIPHENYLS (PCBs)

### STUDIES USING RADIOACTIVE-LABELED PCBs

#### TISSUE DISTRIBUTION

Using pure  $^{14}\text{C}$ -labeled PCBs, more detailed data on tissue distribution can be obtained. Labeled 2,4,5,2',5'-pentachloro-BP was given orally to mice by Berlin et al. (1975) who found radioactivity to rapidly enter the circulation to be distributed largely to:

- 1) Liver.
- 2) Kidneys.
- 3) Lungs.
- 4) Adrenals.

They found radioactivity to be maximum in the fat within 4-24 hrs, and to have a special affinity for the skin, the bronchiolar epithelium of the lungs, and certain glandular secreting tissue.

#### EXCRETION

Radioactivity appeared in the bile and was excreted in the feces shortly after administration. Matthews and Anderson (1975b) found that in rats given intravenous (i.v.) doses of the same  $^{14}\text{C}$ -labeled PCB, greater than 90% was removed from blood within 10 minutes, with most of the radioactivity deposited initially in the liver and muscle and later transferred to skin and fat. They found metabolism was a prerequisite for excretion, primarily via bile and less than 7% was found in the urine after 8-9 days.

### TRITIUM-LABELED PCB STUDY

Petersen et al. (1976) studied the absorption, distribution and excretion of two  $^3\text{H}$ -labeled (tritium-labeled) PCBs, 2,5,2',5'-

tetra (TCB) and 2,4,5,2',4',5'-hexachlorobiphenyl (HCB) in rats.

#### DISTRIBUTION

The distribution, 24 hours after oral dosage, of  $^3\text{H}$  remaining in tissues, as percentage of dose, for both isomers, was highest in:

- 1) Skeletal muscle.
- 2) Skin.
- 3) Liver.
- 4) Small intestine.

#### EXCRETION

The major difference was in biliary excretion where 42.2% of TCB was excreted by male and 25.7% by female, while for HCB only 0.5% was excreted by male and 1.1% by females. This difference was attributed to a slower rate of HCB metabolism due to the chlorines in the 4,4'-positions in HCB.

Urinary excretion was of minor significance for both PCBs. They found absorption, distribution and excretion, generally, to be similar in both sexes.

Yakushiji et al. (1979) found relatively large amounts of tri- and tetrachloro-BPs in human milk with these having 4,4'-substitution patterns except for 2,5,2',5'-tetrachloro-BP. Of the 15 major peaks identified in human milk, 12 had 4,4'-substitution patterns and two had one 4-substitution. This finding emphasizes the importance of chlorine position on persistence.

### SUMMARY OF STUDIES

Hansen (1979) summarized much of the data related to this section when he concluded that:

- 1) Absorption of different PCB components varies not only with chemical structure but with gastrointestinal physiology.
- 2) Distribution rates and patterns of PCB components within the animal differ when the components are part of a commercial mixture or when they are administered as pure materials.
- 3) PCB residue disappearance rates are dependent on absorption, metabolism, distribution and excretion, all of which are variable from PCB congener to congener and from species to species.

### CARCINOGENICITY

Cancer is an uncontrolled growth of abnormal forms of cells and a chemical carcinogen is a chemical which can produce a cancer or carcinoma. Various studies have indicated that PCBs, as a group, are considered to be carcinogens.

There are several stages of cancer development leading to tumors which may become malignant.

### YUSHO DEATHS DUE TO MALIGNANT NEOPLASMS

Up to Sept. 1973, 22 deaths had occurred among 1200 Yusho patients in Japan, with nine of these deaths diagnosed as being due to malignant neoplasms (tumors), or 41% of the deaths (Kuratsune, 1976). This is suggestive of an excess mortality due to these tumors; however, no conclusive evidence for PCB involvement is available.

### STUDIES OF LIVER TUMORS IN ANIMALS

Ueda (1976) reported on studies in Japan where induction of hepatomas (liver

tumors) occurred in 7 of 12 mice fed 500 ppm of Kanechlor 500 for 32 weeks. No tumors were found at lower levels of KC-500 or with KC-300 and 400 or in control animals. The involvement of PCDFs or PCQs in these tumors is unknown.

### SYNERGISTIC EFFECT OF PCBs WITH OTHER CHEMICALS IN TUMOR PRODUCTION

Additional studies (Ueda, 1976) indicated a synergistic effect for liver tumor induction when mice were fed PCBs and  $\alpha$ -benzene hexachloride, an isomer of the insecticide lindane. He reported that either chemical alone at the same levels did not lead to hepatoma formation.

Jonsson et al. (1981) found that rats fed both DDT and PCB (Aroclor 1242) at 75 ppm caused atypical centrilobular degeneration of the liver, occasionally forming nodules resembling small tumors.

Nishizumi (1976) found that the incidence of liver tumors produced in rats by N-nitrosodiethylamine was enhanced by subsequent dosing with KC-500.

These, and other studies, indicate that PCBs can have a synergistic effect with other chemicals in tumor formation.

### CARCINOMAS AND NEOPLASTIC NODULES

Kimbrough (1976) summarized her work by reporting that in the mouse, neoplastic nodules (hepatomas, hyperplastic nodules) developed after dietary exposure to Aroclor 1254. She also found that female rats, fed 100 ppm Aroclor 1260 for 21 months, developed hepatocellular carcinomas as well as neoplastic nodules in the liver. She also reported adenofibroses (fibroid changes in a gland) of the liver in both mice and rats, a persistent lesion which does not disappear after cessation of PCB exposure.



Neoplastic nodules are a part of the spectrum of response to hepatocarcinogenic agents and must be included in the evaluation of tumorigenesis. The significance of adenofibrosis (cholangiofibrosis) to the development of hepatocarcinomas is not understood to date (Kimbrough, 1979). It also is unknown whether hepatic porphyria is related to the induction of hepatocellular carcinomas (Kimbrough, 1979).

#### CARCINOMAS AND ADENOCARCINOMAS OF GASTROINTESTINAL TRACT

Other studies have summarized research on carcinogenic effects (NIOSH, 1977; IARC, 1978; WHO, 1976; Higuchi, 1976) most of which have been centered on the liver. Additional studies by NCI (1978), however, have found a few carcinomas (malignant new growth made up of epithelial cells) and adenocarcinomas (carcinoma made up of glandular tissue) of the gastrointestinal tract in rats treated with Aroclor 1254 for 104-105 weeks while none were seen in control animals. Hepatocellular hyperplastic nodules were observed in 11/48, 17/46 and 29/48 rats at 25, 50, or 100 ppm in their diet, respectively, with none in control animals.

### TERATOGENICITY

#### PCBS IN EMBRYONIC AND FETAL TISSUES

PCBs have been found in embryonic and fetal tissues of humans (Shiota et al., 1973), experimental animals (Takagi et al., 1976; Vodienik and Lech, 1980) and monkeys (Allen and Barsotti, 1970) after exposure of the pregnant mother; and although considerably more PCBs are transferred to nursing offspring via the

mammary glands than to fetuses via the placenta (above citations), the potential for direct teratogenic (pertaining to the production of physical defects of offspring in utero) effects exist.

#### STUDIES SHOWING NO TERATA

NIOSH (1977) reviewed a number of Japanese publications which indicated that no terata (a fetus or infant with pronounced developmental anomalies as to be considered grotesque; monster) were reported in Yusho babies at birth.

No terata were reported in the two-generation feeding study of PCBs to rats by Linder et al. (1974) using Aroclor 1254 and 1260 up to 100 ppm. Allen and Norback (1976) reported no terata in monkeys fed 2.5 or 5.0 ppm for 6 months prior to breeding although over half the animals aborted.

#### BIRTH DEFECTS IN MICE AFTER SUBCUTANEOUS INJECTION

In mice injected subcutaneously with PCBs for 10 days from day 6 of gestation, various teratogenic effects were found by Watanabe and Sugahara (1981). They reported cleft palate formation which they attributed to specific effects of PCBs and not to its general toxicity. Cleft lip, brachydactyly (short digits) and syndactyly (webbing between digits) also were found. Their results demonstrated a teratogenic effect of PCB in strain ddY mice after subcutaneous injection.

#### TERATOGENIC POTENTIAL FOR PCBs IN HUMANS

Although no terata have been reported to this author's knowledge in primates,

man or monkey, these data do indicate there is teratogenic potential for PCBs in humans, and additional studies in this area are needed.

## EFFECTS ON DIGESTIVE SYSTEM

### PROLIFERATIVE LESIONS FROM CHRONIC EXPOSURE

McConnell and Moore (1979) concluded that proliferative lesions of the gastrointestinal tract are a feature of especially chronic exposure to PCBs by non-human primates.

#### HYPERPLASIA

The initial response in the gastric mucosa was a loss of parietal cells with replacement by mucus-secreting cells accompanied by hyperplasia (increased number of normal cells) with subsequent invasive downgrowth of the glandular epithelium into subjacent tissues.

#### INDICATIONS OF CARCINOGENIC POTENTIAL

Hyperplasia and dysplasia are considered to be the first and second stages, respectively, of cancer formation.

Allen and Norback (1973) found that male rhesus monkeys fed a diet containing 300 ppm of Aroclor 1248 for 3 months developed edematous thickening (several fold) of the stomach wall and marked hypertrophy (cell enlargement) of the pyloric and fundic areas of the gastric mucosa (Figs. 7 & 8). Each treated monkey showed widespread penetration of the muscularis mucosa and invasion of the mucosal epithelium in the stomach. They found the hypertrophy, hyperplasia, and

dysplasia (alteration in size, shape and organization of adult cells) of the gastric mucosa to be short of neoplastic transformation but indicative of the carcinogenic potential of PCBs.

#### SIMILAR EFFECTS FROM SINGLE ORAL DOSE

In a later study, Allen et al. (1974) reported similar effects on the same animals given a single oral dose of 1.5 or 3.0 g/kg of body weight of Aroclor 1248. By 14 days, gastric hypertrophy and hyperplasia and focal ulceration of the stomach lining (Fig. 8) were prominent lesions. Kimbrough (1974) reported ulceration of the gastric and duodenal mucosa in rats given single oral doses of 3 g/kg of either Aroclor 1254 or 1260.

#### DOWNGROWTH OF MUCOUS GLANDS IN FATAL DOSE

McNulty (1976) found extensive downgrowth of mucous glands into the submucosa (Fig. 8) of the stomach of a rhesus monkey who died after 8 months on a diet containing only 3 ppm of Aroclor 1242. Becker et al. (1979) reported total mucous conversion of the gastric epithelium, growth of the gastric glands down through the muscularis mucosae into the submucosa and eventually the formation of cysts lined by mucus-secreting columnar epithelial cells in monkeys fed 1242 at 2-100 ppm in their diets.

McNulty et al. (1980) and Silverman et al. (1979) tested 3,4,3',4'-tetrachloro-BP on immature monkeys fed 3.0 ppm, later reduced to 0.3 ppm, in their diets. They also found gastric hyperplasia to result. The former paper reported no effect for the 2,5,2',5'-isomer also tested; but the 3,4,3',4'-isomer caused the simian analog

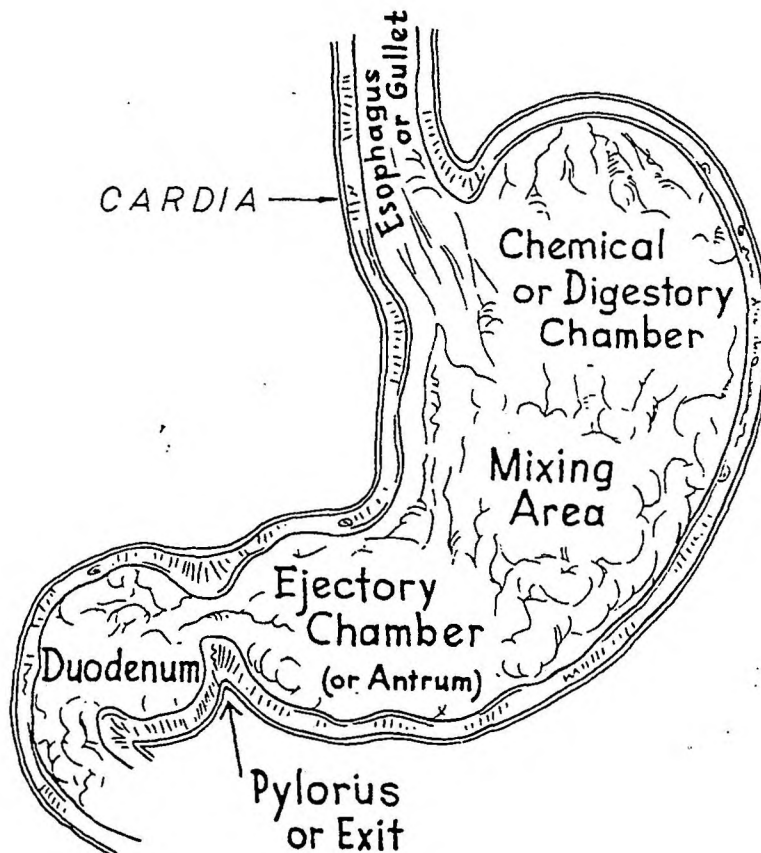


FIG. 7. Diagrammatic Sketch of Normal Stomach and Duodenum

The stomach is the most dilated part of the digestive tube, situated between the end of the esophagus and the beginning of the small intestine. The opening communicating with the duodenum is known as the pyloric orifice; the opening which communicates with the esophagus is the cardiac orifice. The fundus of the stomach is the musculomembranous expansion of the alimentary canal between the esophagus and duodenum. The antrum is a short, conical portion of the stomach with its base contiguous with the orifice of the stomach.

of chloracne in humans (swelling and reddening of the eyelids due to squamous metaplasia of the meibomian glands), weight loss, and death in 1 to 6 months. The latter paper reported that autopsy of 2 of the monkeys that died revealed a broad thick lesion occupying portions of the body and antrum (Fig. 7) of the stomach.

#### PCB POISONING OUTBREAK FROM CONCRETE SEALANT

A spontaneous outbreak of PCB poisoning in rhesus monkeys was reported by Altman et al. (1979) and McConnell et al. (1979) due to PCBs present in the concrete sealant on the cage floors. The former



## TRAUMA

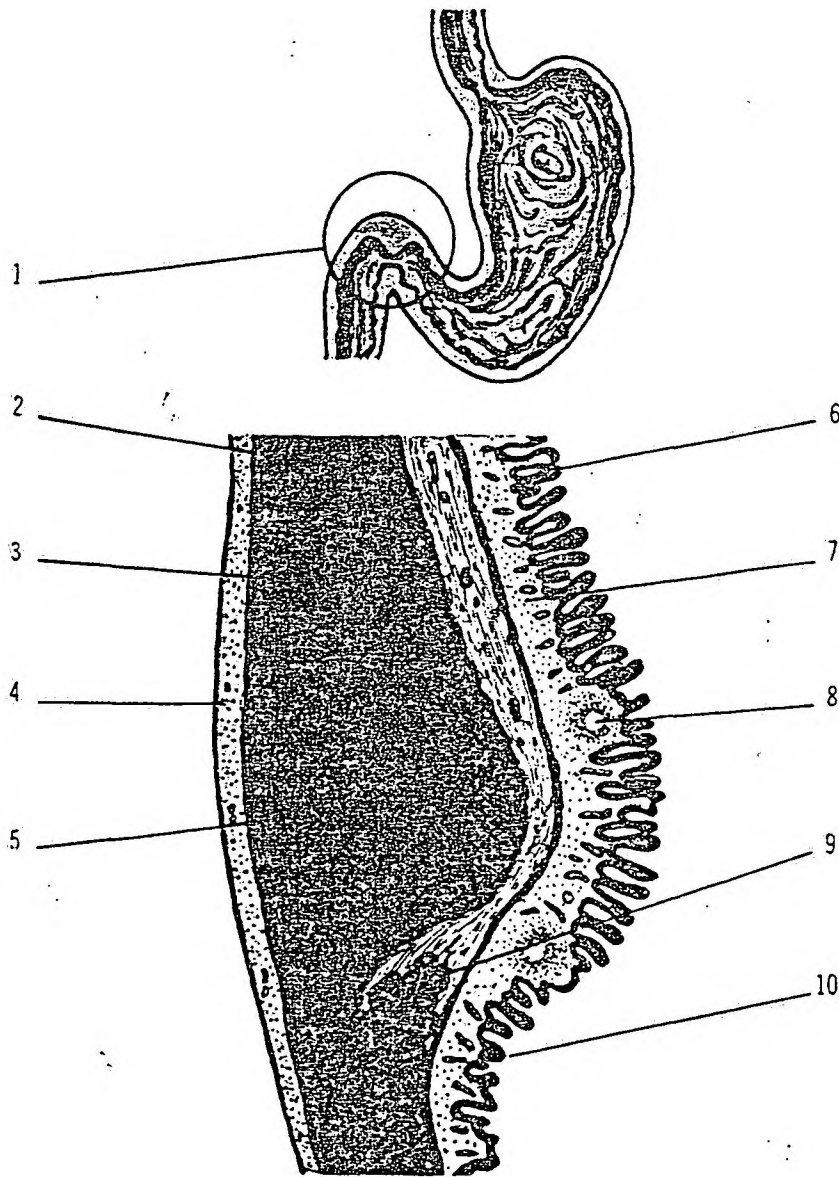


FIG. 8. Diagrammatic Sketch of Gastroduodenal Junction

The stomach is lined by a mucous membrane, which is permeated by tubular glands throughout its entire length. The glands differ in their cell structure and also in their secretions. The layers below the mucous lining or coat are the submucous coat, a muscular coat, and an outer peritoneal or serous coat. The duodenum is the first portion of the intestinal tract. The gastroduodenal junction is shown in the small, upper drawing (1), and the cell structures (histology) of this area are shown in the lower drawing.

paper reported a high incidence of abortions and stillbirths with a high infant mortality rate. The latter paper reported severe hypertrophy of the glandular stomach and a similar but less severe lesion in the colon.

#### YUSHO VICTIMS: SOME DIGESTIVE COMPLAINTS

These studies point out the sensitivity of rhesus monkeys to PCBs. It is not known at this time if humans develop similar digestive lesions; but early reports of nausea, anorexia, etc. may point to some effects in the Yusho victims.

### VITAMIN EFFECTS

#### VITAMIN A: PCB EFFECTS ON STORAGE AND UTILIZATION

Several groups of researchers have been investigating the effects of PCBs on vitamin storage and utilization in light of data that showed that some chemically related insecticides (e.g., DDT and dieldrin) had an effect on liver storage of vitamin A. One of the first studies to report such an effect was Villeneuve et al. (1971) who found that pregnant rabbits dosed with Aroclor 1254 (1 and 10 mg/kg) had about half of the normal hepatic vitamin A values. Cecil et al. (1973) found similar effects in male and female rats and Japanese

quail fed Aroclor 1242 at 100 ppm in the diet.

#### EFFECTS ON GROWTH

Innami et al. (1974) described a study showing significantly decreased hepatic A content in rats fed a 0.1% PCB diet (PCB unspecified). They found that rats given a vitamin A deficient diet with 0.1% PCB showed a significant growth retardation when compared to rats given a normal diet with 0.1% PCB. They also reported that rats fed a 0.1% PCB diet supplemented with vitamin A (3,400 IU) showed better growth than those given a PCB diet alone which indicated that vitamin A supplementation prevented, to some extent, the growth retardation by PCBs. They concluded that PCB-fed rats required more vitamin A than usual and that this vitamin may play a role in PCB detoxication.

#### SKIN APPLICATIONS AMELIORATED HUMAN CHLORACNE

Calabrese (1980) reviews other PCB-related work on vitamin A and reported that vitamin A skin applications had an ameliorative effect on human chloracne due to PCB exposure.

#### B VITAMINS

There are very few reports of PCB effects on the B vitamins. Fugiwara and

FIG. 8. Diagrammatic Sketch of Gastroduodenal Junction  
—continued (see page 2: 104)

- |                            |                                 |
|----------------------------|---------------------------------|
| 1) Gastroduodenal junction | 6) Gastric mucosa               |
| 2) Circular muscle         | 7) Submucosa                    |
| 3) Longitudinal muscle     | 8) Lymphoid nodule              |
| 4) Peritoneum              | 9) Brunner's glands             |
| 5) Pyloric sphincter       | 10) Mucous membrane of duodenum |

Kuriyama (1977) studied PCB effects on pyridoxal phosphate (vitamin B<sub>6</sub>) and riboflavin (B<sub>2</sub>). They fed a mixture of KC-300 to 600 to male rats (10 and 100 mg/kg) for 4 weeks and found no significant changes in riboflavin tissue content but found that PCBs did cause a marked reduction in B<sub>6</sub> liver levels. They suggested that this decrease in B<sub>6</sub> levels may be associated with skin-lesions observed in PCB poisoning, such as chloracne.

Other reports summarized by Calabrese (1980) indicated that deficiencies of thiamine and B<sub>6</sub> enhance the toxicity of PCBs.

## VITAMIN C

### DEFICIENCY IMPAIRS METABOLISM OF INSECTICIDES

Street and Chadwick (1975) reported that a dietary deficiency of vitamin C (ascorbic acid) in guinea pigs impaired the metabolism of a variety of chlorinated pesticides, such as DDT.

Guinea pigs share with primates (apes, monkeys, and man) the inability to synthesize their own dietary requirements of vitamin C so their requirements must be met by dietary inputs. Zannoni and Sato (1975) found that low levels of dietary vitamin C in guinea pigs resulted in a decreased capacity to induce hepatic microsomal enzymes which suggested that this could be the cause of decreased chlorinated pesticide metabolism.

### REDUCTION OF PCB TOXICITY

Chakraborty et al. (1978) reported data that indicated that vitamin C could reduce PCB toxicity by increasing the metabolism and excretion of PCBs. Kato et al. (1977) found that the dietary addition of 2000 ppm of ascorbic acid to guinea pigs fed 500 ppm

Aroclor 1248 significantly prevented PCB-induced growth retardation when compared with animals on diets with only 50 ppm vitamin C. Calabrese (1977) and Fujiwara and Kuriyama (1977) concluded that PCB exposure resulted in an increase in hepatic metabolism of vitamin C which may be associated with an adaptive increase (induction) in detoxification mechanisms. Calabrese (1977) also indicated that a possible cause of PCB toxicity may be due to insufficient conjugate formation, via glucuronides, of hydroxyl metabolites of PCBs. Chakraborty et al. (1978) showed that vitamin C supplementation (20 mg/100 g/day) provided protection against PCB-induced alterations in hepatic vitamin C metabolizing enzymes and some histological liver damage.

### ROLE OF VITAMIN C IN DETOXIFICATION OF CARCINOGENS AND DRUGS

Calabrese (1980) reviewed some additional data and concluded that vitamin C metabolism is not only altered by PCBs but that L-ascorbic acid can prevent some of the PCB-induced toxicity symptoms. He concluded further that "the evidence is clear that dietary ascorbic acid does play an important role in the detoxification of certain drugs and carcinogens within guinea pigs, a species which, like humans, does not synthesize its own ascorbic acid."

It can be assumed that humans will exhibit a similar dependency on ascorbic acid for these functions.

### FEW STUDIES ON NUTRITIONAL FACTORS AFFECTING PCB TOXICITY

It is apparent that much more research needs to be done on the potential protective effects of vitamin supplementation to PCB-exposed or poisoned persons. It should be



apparent that despite hundreds of papers on PCB toxicity, there are very, very few on nutritional factors that may affect its toxicity. The compendium by Calabrese (1980) is a valuable contribution to this general area.

## SUMMARY AND CONCLUSIONS

### LARGE RESERVOIR OF PCBs

It can be approximated that from 1929 through much of 1977, approximately 1,000,000 tons of PCBs have been produced world-wide with the large majority produced in the U.S.

Estimates, ranging up to half of this total, place much of this production as already existent in various environmental compartments, including landfills, dumps, fresh and marine waters, air, sediments and in the tissues of various life forms.

Most of the remainder apparently is still in service, primarily in transformers and capacitors, while only relatively low quantities have been destroyed either biologically, chemically, or thermally. There thus remains a large reservoir of PCBs world-wide, especially in the U.S., which are potentially capable of entering the mobile environment. Hopefully, the 1976 passage of the Toxic Substances Control Act and rigorous enforcement of its specifications, coupled with terminated PCB production, can minimize environmental inputs of PCBs.

### POTENTIAL EFFECTS THROUGH LOW-LEVEL, CHRONIC EXPOSURES

Although the PCBs have relatively low acute toxicity, their potential and real dele-

terious effects are through relatively low-level, chronic exposures. Thousands of papers describing their distribution, toxicity, metabolism, health effects, etc. are in the literature today and yet much still needs to be known.

### COMPLEX NATURE OF PCBs

The complex nature of a commercial PCB, not uncommonly consisting of more than 70 components, makes it an exceedingly arduous chore for researchers to sort out the effects due to a single PCB.

### POSSIBLE SYNERGISTIC EFFECTS

Compounding this problem are the possible synergistic effects, some already known, which may occur between PCBs and other environmental pollutants, such as pesticides, or with drugs, food additives, and other chemical compounds.

### METABOLISM TO POTENTIAL CARCINOGENS OR TOXIC EFFECTS FROM PCBs IN TISSUES

Two adjacent unsubstituted carbon atoms in the PCB molecule are important in the metabolism of PCBs since it facilitates the formation of arene oxides by the MFO of the liver, metabolic intermediates implicated as potential carcinogens. This poses a dilemma because those PCB congeners which can be metabolized and excreted rapidly may do so via a carcinogenic intermediate, whereas those which are not metabolized readily are extremely persistent in body tissues and may exert other toxic effects, as noted for the common 2,4,5,2',4',5'-hexachlorobiphenyl isomer, such as chloracne, liver damage and hepatic porphyria.

## MORE RESEARCH ON NON-HUMAN PRIMATES NEEDED

Most of the research on PCB effects has been done with rodents, such as mice and rats, some on guinea pigs, chickens, and rabbits, and relatively little on mammals most closely related to man, the non-human primate. Yet it appears that rhesus monkeys are very susceptible to PCB intoxication at much lower dose levels than mice or rats and the effects are more pronounced, aside from liver effects. Certainly, more research on PCBs should be directed toward use of such a non-human primate.

### SEVERE PCB INTOXICATION FROM LEVELS NOT MUCH HIGHER THAN FDA PERMITTED LEVELS

In addition, severe PCB intoxication has been shown to occur in chronic feeding studies with these monkeys at levels not much higher than FDA permitted levels in some human foods. It has also been shown that monkeys and humans display similar signs and lesions of PCB intoxication.

## TOXICITY OF CONTAMINANTS

Besides the PCBs themselves, a serious cause for concern are the impurities found to be present in commercial samples—the PCNs, the PCDFs, and more recently the PCQs. While the PCNs generally are slightly less toxic than PCBs, the PCDFs are up to several hundred fold more toxic, while essentially nothing is known of the PCQs. In addition, it is known from the Yusho incident and other research, that PCDFs are often in considerably greater concentration in used or aged PCBs than in unused commercial samples.

## OVERT EFFECTS EASILY OVERLOOKED

PCBs are known to cause various overt effects that are easily overlooked or not investigated. These include both neurological and behavioral effects, endocrine and reproductive effects, effects on both the lungs and the immune system, carcinogenic and mutagenic effects and even changes in vitamin levels.

## MUST CONTROL DISPOSAL OF PCBS

Disposal of used PCBs must be carefully controlled to not only prevent continued release of PCBs into the environment but also to prevent the additional formation of the toxic PCDFs by improper combustion.

The book on PCBs is far from being closed. The ban on manufacture of PCBs should not deter research to be continued on their effects on animals, especially monkeys, and also the humans who are accidental poisoning victims. PCB residues in the environment will be with us for many years to come, as will the ramifications of their effects on various organisms, because of the vast amount of PCBs still extant in the environment today.

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