Toxicological Profile for

SELECTED PCBs (AROCLOR-1260, -1254, -1248, -1242, -1232, -1221, and -1016)



Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

Comment Period Ends:

MONS 027268

DRAFT

TOXICOLOGICAL PROFILE FOR SELECTED PCBs (Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016)

Date Published — November 1987

Prepared by:

Syracuse Research Corporation
under Contract No. 68-03-3228

for

Agency for Toxic Substances and Disease Registry (ATSDR)
U.S. Public Health Service

in collaboration with

U.S. Environmental Protection Agency (EPA)

Published by:

Oak Ridge National Laboratory
under
DOE Interagency Agreement No. 1425-1425-A1

MONS 027269

DISCLAIMER

Mention of company name or product does not constitute endorsement by the Agency for Toxic Substances and Disease Registry.

MDNS 027270

FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

MONS 027271

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

James O. Mason

James O. Mason, M.D., Dr. P.H.
Assistant Surgeon General
Administrator, ATSDR

MONS 027272

CONTENTS

FOREWORD iii

LIST OF FIGURES vii

LIST OF TABLES ix

1. PUBLIC HEALTH STATEMENT 1
   - 1.1 WHAT ARE PCBs? 1
   - 1.2 HOW MIGHT I BE EXPOSED TO PCBs? 1
   - 1.3 HOW DO PCBs GET INTO MY BODY? 2
   - 1.4 HOW DO PCBs AFFECT MY HEALTH? 2
   - 1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO PCBs? 2
   - 1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS? 2
   - 1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 3

2. HEALTH EFFECTS SUMMARY 7
   - 2.1 INTRODUCTION 7
   - 2.2 LEVELS OF SIGNIFICANT EXPOSURE 8
     - 2.2.1 Key Studies and Graphical Presentations 8
     - 2.2.2 Biological Monitoring as a Measure of Exposure and Effects 20
     - 2.2.3 Environmental Levels as Indicators of Exposure and Effects 27
   - 2.3 ADEQUACY OF DATABASE 28
     - 2.3.1 Introduction 28
     - 2.3.2 Adequacy of the Database for Health Effect End Points 29
     - 2.3.3 Adequacy of the Database for Other Information Needed for Risk Assessment 32

3. CHEMICAL AND PHYSICAL INFORMATION 35
   - 3.1 CHEMICAL IDENTITY 35
   - 3.2 PHYSICAL AND CHEMICAL PROPERTIES 35

4. TOXICOLOGICAL DATA 41
   - 4.1 OVERVIEW 41
   - 4.2 TOXICOKINETICS 43
     - 4.2.1 Absorption 43
     - 4.2.2 Distribution 44
     - 4.2.3 Metabolism 46
     - 4.2.4 Excretion 48

MONS 027273

4.3 TOXICITY 49
4.3.1 Lethality and Decreased Longevity 50
4.3.2 Systemic/Target Organ Toxicity 52
4.3.3 Developmental Toxicity 62
4.3.4 Reproductive Toxicity 65
4.3.5 Genotoxicity 66
4.3.6 Carcinogenicity 66
4.4 INTERACTIONS WITH OTHER CHEMICALS 73

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL 75
5.1 OVERVIEW 75
5.2 PRODUCTION 75
5.3 IMPORT 75
5.4 USES 76
5.5 DISPOSAL 76

6. ENVIRONMENTAL FATE 77
6.1 OVERVIEW 77
6.2 RELEASES TO THE ENVIRONMENT 77
6.3 ENVIRONMENTAL FATE 78
6.3.1 Transport and Partitioning 78
6.3.2 Transformation and Degradation 79

7. POTENTIAL FOR HUMAN EXPOSURE 81
7.1 OVERVIEW 81
7.2 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 81
7.2.1 Air 81
7.2.2 Water 82
7.2.3 Soil 82
7.2.4 Other 83
7.3 OCCUPATIONAL EXPOSURES 85
7.4 POPULATIONS AT HIGH RISK 87

8. ANALYTICAL METHODS 89
8.1 ENVIRONMENTAL MEDIA 89
8.2 BIOMEDICAL SAMPLES 89

9. REGULATORY AND ADVISORY STATUS 93
9.1 INTERNATIONAL 93
9.2 NATIONAL 93
9.2.1 Regulations 93
9.2.2 Advisory Guidance 93
9.2.3 Data Analysis 94
9.3 STATE 95

10. REFERENCES 97

11. GLOSSARY 123

APPENDIXES
A. PEER REVIEW 129
B. *FEDERAL REGISTER* ANNOUNCEMENT 131

MONS 027274

LIST OF FIGURES

1.1 Health effects from breathing PCBs 4

1.2 Health effects from ingesting PCBs 5

1.3 Health effects from skin contact with PCBs 6

2.1 Effects of PCBs--inhalation exposure 9

2.2 Effects of PCBs--oral exposure 10

2.3 Effects of PCBs--dermal exposure 11

2.4 Levels of significant exposure for PCBs--inhalation 12

2.5 Levels of significant exposure for PCBs--oral 13

2.6 Levels of significant exposure for PCBs--dermal 14

2.7 Adequacy of the database on health effects of PCBs (human data) 30

2.8 Adequacy of the database on health effects of PCBs (animal data) 31

MONS 027275

LIST OF TABLES

2.1 PCB levels in blood of exposed workers (Aroclors 1016, 1242, 1248) 21

2.2 PCB blood levels (Aroclor 1254) and duration of exposure 23

2.3 Serum PCB concentrations in U.S. populations without occupational exposure to PCBs and in subpopulations consuming fish from PCB-contaminated waters 24

2.4 Serum PCB concentrations in populations with occupational exposure 26

3.1 Chemical identity of the Aroclors 37

3.2 Physical and chemical properties of PCBs 38

3.3 Approximate molecular composition of PCBs 40

4.1 Acute oral LD_{50}s of Aroclors 51

4.2 Acute dermal LD_{50} values of Aroclors in rabbits 53

4.3 Genotoxicity of PCBs in vitro 67

4.4 Genotoxicity of PCBs in vivo 68

7.1 Aroclor residues in raw domestic agricultural commodities for fiscal years 1970-1976 84

7.2 Estimated dietary intake of PCBs for adults, infants, and toddlers (μg/kg/day) 86

8.1 Analytical methods for environmental media 90

8.2 Analytical methods for biological samples 91

MONS 027276

1. PUBLIC HEALTH STATEMENT

1.1 WHAT ARE PCBs?

The abbreviation PCB refers to polychlorinated biphenyls. PCBs are a family of man-made chemicals that contain 209 individual compounds. Because of their insulating and nonflammable properties, they have been used widely as coolants and lubricants in transformers, capacitors, and other electrical equipment. The industrial manufacture of PCBs was stopped in the United States in October 1977 because it had been discovered that PCBs would accumulate and persist in the environment and could cause toxic effects. Some commercial PCB mixtures are known in the United States by their industrial trade name, Aroclor.

1.2 HOW MIGHT I BE EXPOSED TO PCBs?

Although PCBs are no longer manufactured, human exposure to these compounds is still occurring. Many of the transformers and capacitors that were filled with fluids containing PCBs when they were made still contain PCBs and are still in service. The useful lifetime of many of these transformers can be 30 years or more.

The two main sources of human exposure to PCBs are environmental and occupational. PCBs are very persistent chemicals that are widely distributed throughout the entire environment. Background levels of PCBs can be found in the outdoor air we breathe, on soil surfaces, and in water. Consumption of contaminated fish is a major source of PCB exposure to humans. Fish become contaminated with PCBs by exposure in water, which results in a very high accumulation of PCBs in the fish tissue. Most of the PCBs in the outdoor air we breathe may be present because of an environmental cycling process. Compared with the intake of PCBs through consumption of contaminated fish, exposure to PCBs as a result of breathing air containing PCBs is negligible. PCBs in water, or on soil surfaces, evaporate into the air and are then returned to earth by rainfall or settling of dust particles containing PCBs. Reevaporation repeats the cycle. Once in the air, PCBs can be carried long distances; PCBs have been found in snow and seawater in the Antarctic.

PCBs can be released into the environment from the following sources:

- Poorly maintained toxic waste sites which contain PCBs
- Illegal or improper dumping of PCB wastes, such as transformer fluids
- Leaks or fugitive emissions from electrical transformers containing PCBs

MONS 027277

Some consumer products that may contain PCBs are:

- Fluorescent lighting fixtures made before PCB use was stopped
- Electrical devices or appliances containing PCB capacitors made before PCB use was stopped

Occupational exposure to PCBs can occur during:

- Repair or maintenance of PCB transformers
- Accidents or spills involving PCB transformers
- Disposal of PCB materials
- Contact at hazardous waste sites

1.3 HOW DO PCBs GET INTO MY BODY?

PCBs can enter the body when food containing PCBs is eaten, when air that contains PCBs is breathed, or when skin comes in contact with PCBs. Most exposure of the general population is by consumption of fish and shellfish from PCB-contaminated water. Exposure from drinking water is minimal. Infants can be exposed to PCBs from breastfeeding if the mothers have PCBs in their breast milk.

1.4 HOW DO PCBs AFFECT MY HEALTH?

Occasional skin irritations, usually acnelike lesions and rashes, and liver effects are the only significant adverse health effects that have been observed in PCB-exposed workers. Workers experience PCB exposures that are much higher than those received by the general public. Adverse health effects have not been observed in people in the United States with nonoccupational exposure. Effects of PCBs in experimentally exposed animals include liver damage, skin irritations, death, low birth weights and other reproductive effects, and cancer.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO PCBs?

PCBs can be detected in the blood, body fat, and breast milk. Blood PCB levels are the best indicator of recent exposure to PCBs, and levels in the fat are the best indicators of long-term exposure. These tests are not routine clinical tests, but they could be used to detect PCBs in members of the general population as well as workers with occupational exposure to PCBs. Although these tests indicate if there has been exposure to PCBs, they cannot be used to predict potential health effects.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The graphs on the following pages show the relationship between exposure to PCBs and known health effects for the PCBs that are covered by this profile. Other PCBs may have different toxic properties. In the first set of graphs, labeled "Health effects from breathing PCBs,"

exposure is measured in milligrams of PCBs per cubic meter of air (mg/m^3). In all graphs, effects in animals are shown on the left side, effects in humans on the right.

In the second set of graphs, the same relationship is represented for the known "Health effects from ingestion of or skin contact with products containing PCBs." Exposures are measured in milligrams of PCBs per kilogram of body weight per day (mg/kg/day).

Figures 1.1, 1.2, and 1.3 show the relationship between exposure to PCBs and known health effects. The scales represent exposure levels. The first column on the graphs, labeled "Short-Term," refers to known health effects from exposure to PCBs for 2 weeks or less. The columns labeled "Long-Term" refer to PCB exposures of longer than 2 weeks. The level marked on Fig. 1.1 as the TLV (threshold limit value) is an average level recommended as a limit for workers over an 8-hour workshift and 40-hour workweek. The levels marked on the graphs as anticipated to be associated with minimal risk of developing health effects are based on information generated from animal studies; therefore, some uncertainty still exists. Based on information that PCBs cause cancer in animals, the Environmental Protection Agency (EPA) considers PCBs to be probable cancer-causing chemicals in humans and has estimated that ingestion of 1 microgram of PCB per kilogram per day for a lifetime would result in 770 additional cases of cancer in a population of 10,000 people and 770,000 additional cases of cancer in a population of 10,000,000 people. It should be noted that these risk values are plausible upper-limit estimates. Actual risk levels are unlikely to be higher and may be lower.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has made recommendations to limit exposure to PCBs in the workplace and exposure of the general public to PCBs in drinking water and food. The National Institute for Occupational Safety and Health (NIOSH) recommends an occupational exposure limit for all PCBs of 0.001 milligram of PCBs per cubic meter of air (mg/m^3) for a 10-hour workday, 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends limits of 0.5-2 mg/m^3 for occupational exposures to specific PCBs (see Fig. 1.1).

EPA recommends that levels in drinking water of 0.0035 milligram PCB 1016 per liter of water (mg/L) for adults and 0.001 mg/L PCB 1016 for children are probably safe. These health advisories are for a specific PCB (1016) because other PCBs have not been detected in drinking water; an exposure period of approximately 7 years is assumed. With respect to cancer, however, it is assumed that "any exposure involves some risk" in the absence of information to the contrary.

The Food and Drug Administration (FDA) specifies PCB concentration limits of 0.2 to 3 parts per million (milligrams PCB per kilogram of food) in foods such as infant foods, eggs, milk (in milk fat), and poultry (fat).

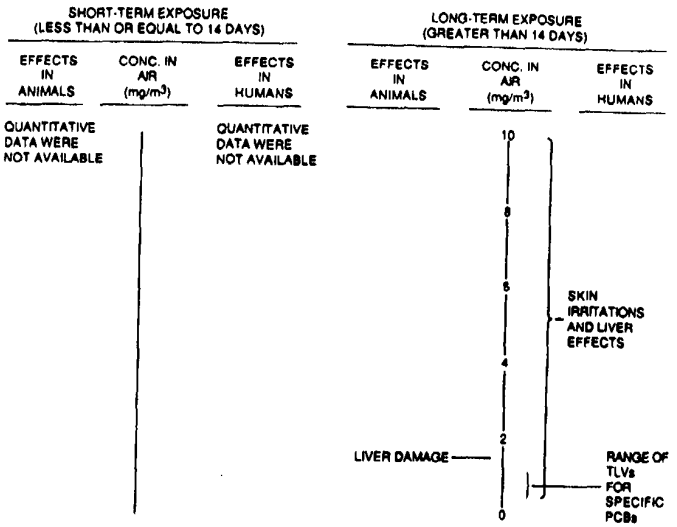


Fig. 1.1. Health effects from breathing PCBs.

MONS 027280

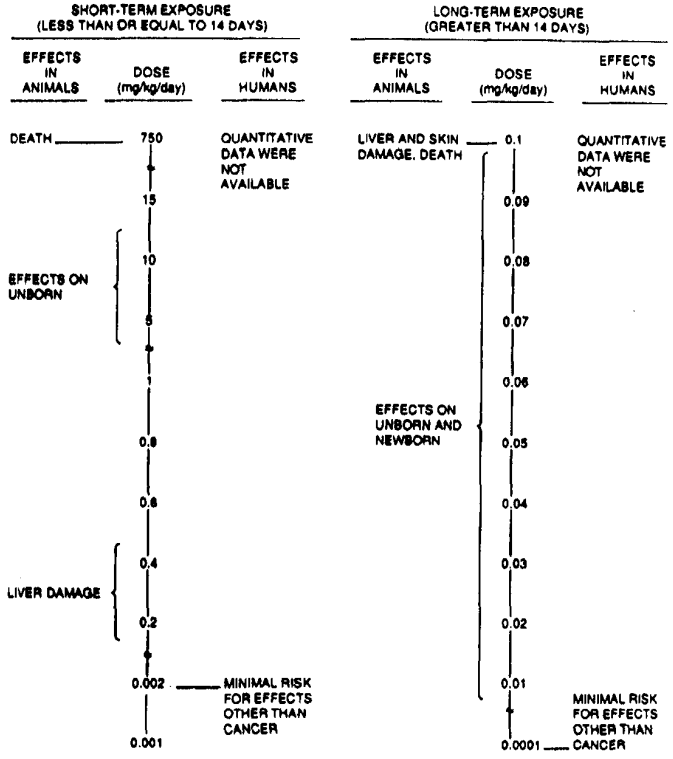


Fig. 1.2. Health effects from ingesting PCBs.

MONS 027281

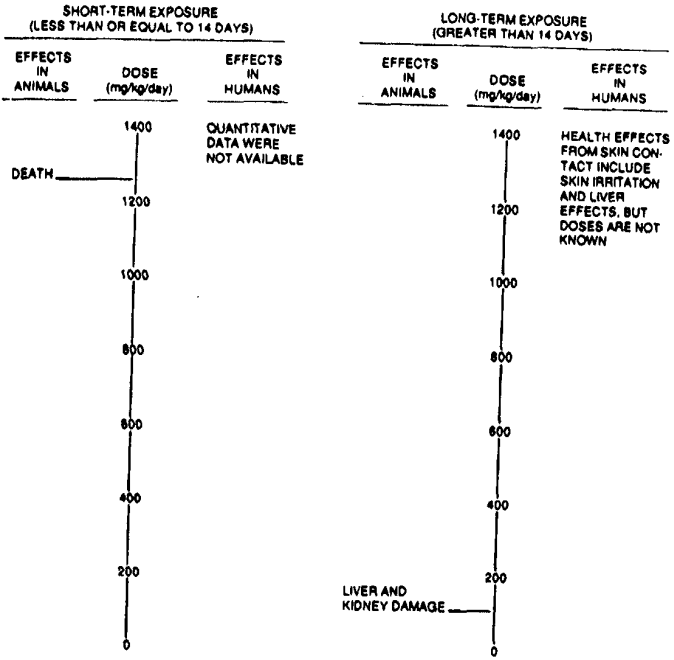


Fig. 1.3. Health effects from skin contact with PCBs.

MONS 027282

2. HEALTH EFFECTS SUMMARY

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to PCBs. The purpose of this section is to present levels of significant exposure for PCBs based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicological Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of PCBs and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of PCBs that have been monitored in human fluids and tissues and information about levels of PCBs found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graph may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level, LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect. 2.3) highlights the availability of key studies on exposure to PCBs in the scientific literature and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest where there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda to provide this information.

MONS 027283

2.2 LEVELS OF SIGNIFICANT EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points (and levels of exposure) for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing NOAELs and LOAELs reflect the actual doses (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol were made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental vs actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. These minimal risk levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these minimal risk levels (Barnes et al. 1987), shortcomings exist in the techniques that reduce the confidence in the projected estimates. Also shown on the graphs under the cancer end point are low-level risks (10^{-4} to 10^{-7}) reported by EPA. In addition, the actual dose (level of exposure) associated with the tumor incidence is plotted.

2.2.1 Key Studies and Graphical Presentations

Dose-response-duration data for the toxicity and carcinogenicity of the PCBs discussed in this profile are displayed in two types of graphs. These data are derived from the key studies described in the following sections. The "thermometer" graphs in Figs. 2.1, 2.2, and 2.3 plot exposure levels vs NOAELs and LOAELs for various effects and durations of inhalation, oral, and dermal exposures, respectively. The graphs of levels of significant exposure in Figs. 2.4, 2.5, and 2.6 plot end point-specific NOAELs, LOAELs, and/or minimal levels of risk for acute (≤14 days), intermediate (15-364 days), and chronic (≥365 days) durations for inhalation, oral, and dermal exposures, respectively. Dermal exposure contributes significantly to occupational exposure, but the relative contributions of dermal and inhalation exposure in occupational settings has not been discerned (Wolff 1985). Furthermore, occupational exposure levels are expressed as concentrations of PCBs in air, making it difficult to quantitate dermal exposure doses. For this

MONS 027284

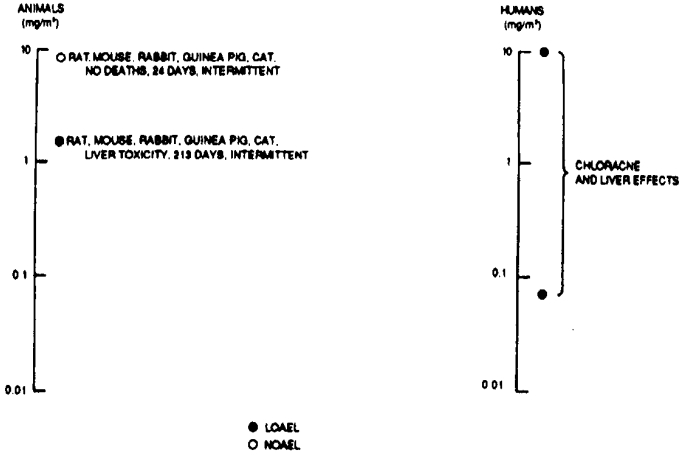


Fig. 2.1. Effects of PCBs—inhalation exposure.

MONS 027285

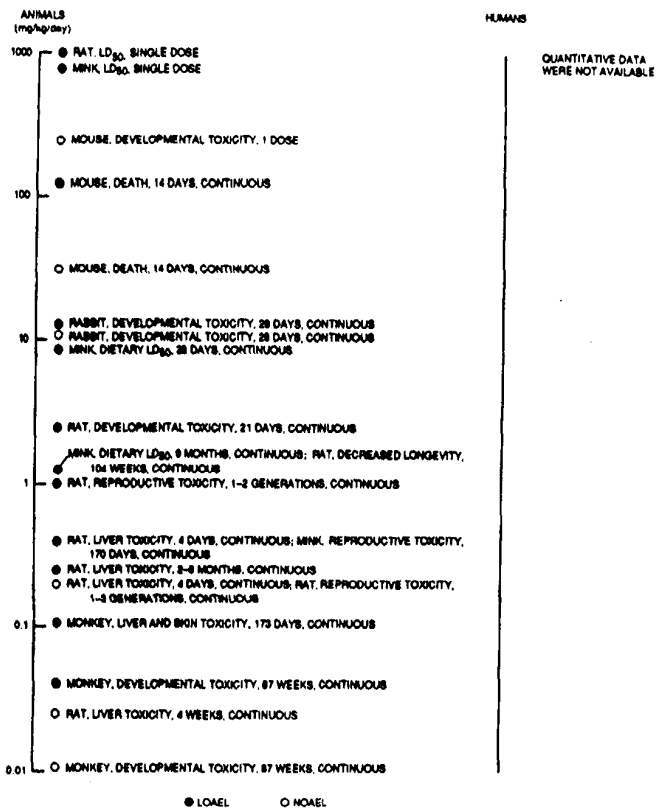


Fig. 2.2. Effects of PCBs—oral exposure.

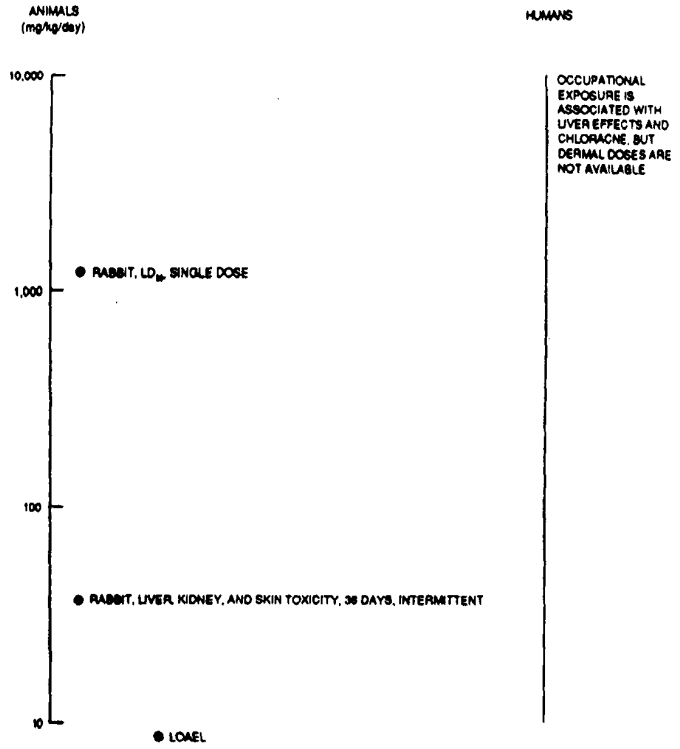


Fig. 2.3. Effects of PCBs—dermal exposure.

MONS 027287

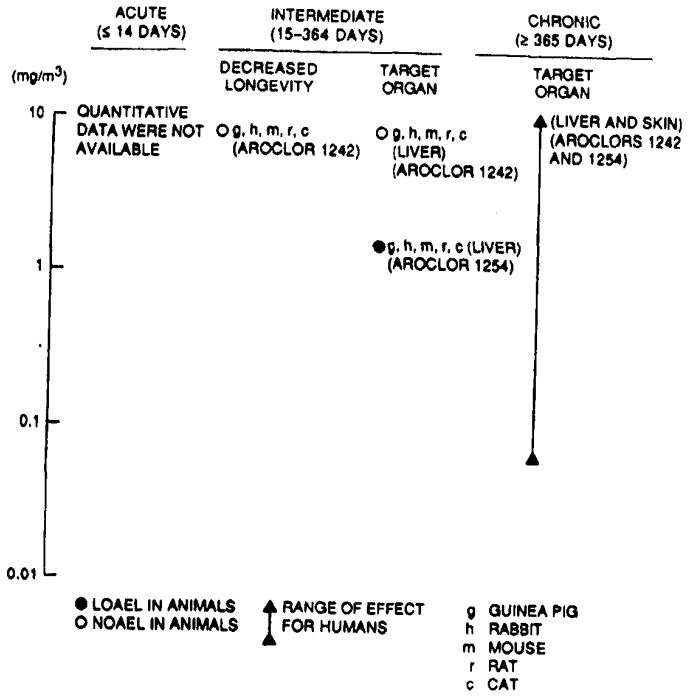


Fig. 2.4. Levels of significant exposure for PCBs—inhalation exposure.

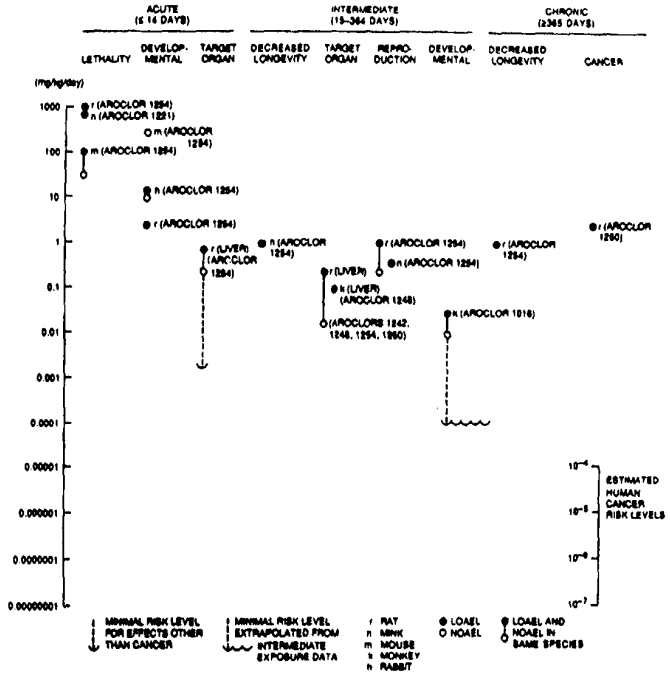


Fig. 2.5. Levels of significant exposure for PCBs—oral.

MONS 027289

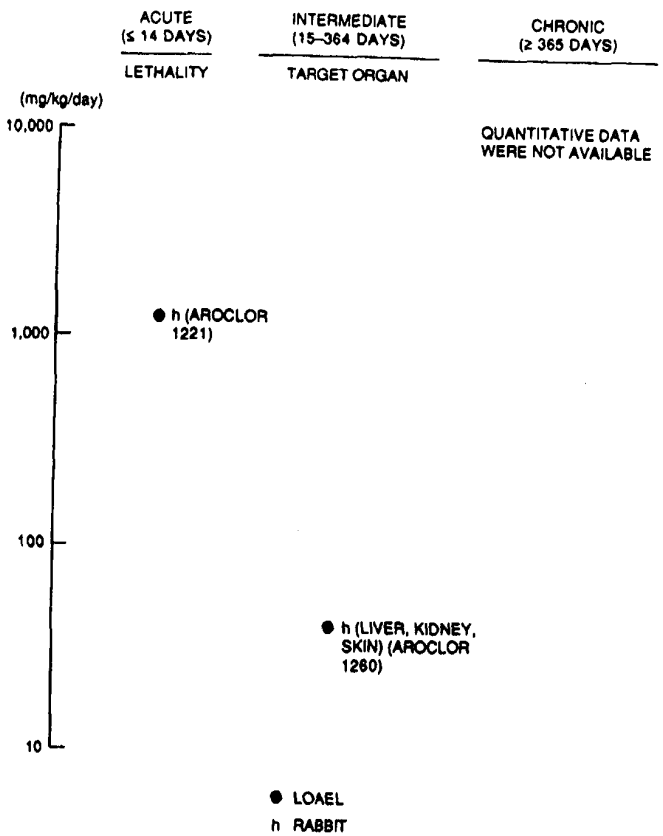


Fig. 2.6. Levels of significant exposure for PCBs—dermal exposure.

reason, effects of occupational exposure are discussed under inhalation exposure and plotted in Figs. 2.1 and 2.4 (graphs for inhalation exposure).

2.2.1.1 Inhalation exposure

Lethality and decreased longevity. Data regarding inhalation exposure levels that produce death in humans were not available. Exposure to near saturation vapor concentrations of heated Aroclor 1242 (8.6 mg/m^3) 7 h/day, 5 days/week for 24 days was not lethal for cats, rats, mice, rabbits, or guinea pigs (Treon et al. 1956). This concentration represents a NOAEL for lethality for intermediate inhalation exposures (see Figs. 2.1 and 2.4). No data were available regarding lethality/decreased longevity of animals due to acute or chronic inhalation exposure to PCBs.

Target organ/systemic toxicity. Oral toxicity studies have established that the liver and cutaneous tissues are primary target organs of PCBs. Occupational exposure to PCBs has been associated with alterations in serum levels of liver enzymes and dermatological effects such as chloracne (Meigs et al. 1954; Ouw et al. 1976; Fischbein et al. 1979, 1982; Baker et al. 1980; Smith et al. 1981a,b,c). Although monitoring data were reported in some of the studies, exposure levels were not adequately characterized. Furthermore, although inhalation exposure is considered a major route of exposure, the contribution of dermal exposure to total occupational exposure is also significant. Fischbein et al. (1979) reported that occupational 8-h time-weighted average (TWA) concentrations of Aroclor 1242 and 1254 ranged from 0.07 to 11.0 mg/m^3 in workers who had increased SGOT levels and skin effects; the range is plotted on Figs. 2.1 and 2.4.

In the only animal inhalation study of PCBs, degenerative liver lesions, a frank effect, occurred in cats, rats, mice, rabbits, and guinea pigs that were exposed to 1.5 mg/m^3 Aroclor 1254 vapor for 7 h/day, 5 days/week for 213 days (Treon et al. 1956). This FEL is plotted on Figs. 2.1 and 2.4. Histologic effects were not produced in those species exposed to Aroclor 1242 (1.9 mg/m^3 7 h/day, 5 days/week for 214 days, 8.6 mg/m^3 7 h/day, 5 days/week for 24 days). The higher NOAEL of 8.6 mg/m^3 for intermediate-duration inhalation exposure is plotted on Fig. 2.4. Since the FEL for Aroclor 1254 is lower than the NOAEL for Aroclor 1242, a minimal risk level cannot be derived.

Developmental toxicity. Pertinent data regarding developmental effects of PCBs via inhalation exposure in animals were not located in the available literature. Slightly lowered mean birth weight and gestational age was observed in infants born to mothers with occupational exposure (dermal and inhalation) to PCBs, but monitoring data were not reported (Taylor et al.1984).

Reproductive toxicity. Pertinent data regarding reproductive effects of PCBs via inhalation exposure in humans or animals were not located.

Genotoxicity. The PCBs have produced generally negative results in in vivo and in vitro genotoxicity assays (Sect. 4.3.5 on genotoxicity in toxicological data section).

Carcinogenicity. An increased incidence of malignant melanomas was reported in a group of workers exposed occupationally (considered inhalation, although dermal exposure is also considered to be likely) to Aroclor 1254 (Bahn et al. 1976). These and other data provide inadequate evidence of carcinogenicity in humans (Sect. 4.3.6 on carcinogenicity in toxicological data section). Data regarding the carcinogenicity of inhaled PCBs in animals were not available.

2.2.1.2 Oral exposure

Lethality and decreased longevity. Data regarding oral exposure levels that produce death in humans were not available. Single-dose oral LD50s for PCBs have been reported for rats and mink. The lowest values are 750 mg/kg for Aroclor 1221 in mink (Aulerich and Ringer 1977) and 1010 mg/kg for Aroclor 1254 in rats (Garthoff et al. 1981). These FELs are plotted on Figs. 2.2 and 2.5 for lethality due to acute oral exposure.

In mice fed diets containing 1000 ppm Aroclor 1254 for 14 days, 3 of 5 died by day 15 (Sanders et al. 1974). No mice fed diets containing 250 ppm Aroclor 1254 for 14 days died. Thus, 250 ppm is a NOAEL, and 1000 ppm is a FEL for lethality in mice for short-term oral exposure. Assuming that a mouse consumes a daily amount of food equal to 13% of its body weight (EPA 1986a), the NOAEL is equivalent to 32.5 mg/kg/day, and the FEL is equivalent to 130 mg/kg/day. These levels are plotted on Figs. 2.2 and 2.5 for lethality for acute oral exposure. Hornshaw et al. (1986) determined LC50s of Aroclor 1254 for dietary expoeure in mink to be 79-84 ppm for 28 days and 47-49 ppm for 28 days followed by a 7-day withdrawal period. In mink fed Aroclor 1254 for 9 months, the LC50 was 6.65 ppm (Ringer et al. 1981). Assuming that mink consume 150 g of feed per day and weigh 800 g (Bleavins et al. 1980), 47 ppm is equivalent to an LD50 of 8.8 mg/kg/day (see Fig. 2.2), and 6.65 ppm is equivalent to an LD50 of 1.25 mg/kg/day. This FEL is plotted on Figs. 2.2 and 2.5 for intermediate exposure.

Reduced survival occurred in rats fed diets containing >25 ppm Aroclor 1254 for 104 weeks (NCI 1978). Assuming that rats consume the equivalent of 5% of their body weight per day in food (EPA 1986a), then 1.25 mg/kg/day represents a FEL for chronic oral exposure in rats (see Figs. 2.2 and 2.5). NOAELs for increased mortality were not identified in these studies.

Target organ/systemic toxicity. The liver and cutaneous tissues are primary targets of PCB toxicity in orally exposed animals.

Increased relative liver weight occurred in rats fed diets containing >8 ppm but not 4 ppm Aroclor 1254 for 4 days (Carter 1985). The 4- and 8-ppm levels, which correspond to 0.2 and 0.4 mg/kg/day, respectively, if rat food consumption is assumed to be 5% of body weight per day, represent a NOAEL and LOAEL for acute oral exposure (see Figs. 2.2 and 2.5). The NOAEL is the basis for the minimal risk level for acute oral exposure (see Fig. 2.5).

In intermediate-duration studies, hepatic microsomal enzyme activities were increased in rats treated with diet concentrations of 0.5, 5, or 50 ppm Aroclors 1242, 1248, 1254, or 1260 for 4 weeks (Litterst et al. 1972). Dietary exposure to 5 ppm Aroclor 1242 for 2 to 6 months produced increased liver lipid content in rats (Bruckner et al. 1974) and >20 ppm Aroclor 1254, or 1260 for 28 days (Chu et al. 1977) or 8 months (Kimbrough et al. 1972) produced frank degenerative liver alterations in rats. Dietary concentrations of 0.5 ppm Aroclors 1242, 1248, 1254, and 1260 and 5 ppm Aroclor 1242, therefore, represent the highest NOAEL and lowest LOAEL, respectively, for intermediate-duration hepatic effects in rats. Assuming that rats consume 5% of their body weight in food per day, the NOAEL and LOAEL provided 0.025 and 0.25 mg/kg/day, respectively (see Figs. 2.2 and 2.5).

Two monkeys that died from dietary exposure to 2.5 or 5.0 ppm Aroclor 1248 for 173 or 310 days, respectively, had frank liver lesions (Barsotti et al. 1976). Although this study is limited by the number of animals, other studies with monkeys corroborate these FELs, as chloracne and gastric lesions were also associated with intermediate-duration exposure to 2.5 or 5.0 ppm Aroclor 1248 (Barsotti and Allen 1975, Barsotti et al. 1976, Thomas and Hinsdill 1978). The lowest monkey FEL (2.5 ppm) is equivalent to 0.105 mg/kg/day (see Figs. 2.2 and 2.5) if it is assumed that monkey food consumption is 4.2% of body weight per day (EPA 1986a).

Chronic feeding studies with rats (NCI 1978; Morgan et al. 1981, Ward 1985, Norback and Weltman 1985, Kimbrough et al. 1975), conducted at concentrations (>20 ppm) that were higher than the lowest FELs in the intermediate-duration monkey studies, did not produce non-preneoplastic or nonproliferative liver lesions. Chronic (12 to 16 month) feeding studies were conducted with 2.5 and 5.0 ppm Aroclor 1248 in monkeys (Barsotti and Allen 1975, Barsotti et al. 1976), but skin lesions and other effects (as indicated above and in subsequent sections) occurred after several months of exposure. Therefore, it is inappropriate to identify effect levels for systemic effects resulting from chronic oral exposure because of the types of liver lesions (preneoplastic) in rats and the short latency for cutaneous and other effects in monkeys.

Developmental toxicity. Slightly decreased birth weight, head circumference, and gestational age were observed in newborns of mothers who were consumers of PCB-contaminated fish, but the effects were not associated with specific levels of intake (Fein 1984, Fein et al. 1984). Rogan et al. (1986) found that levels >3.5 ppm PCBs in milk fat were significantly correlated with decreased muscle tone, decreased activity, and abnormal reflexes in human infants. Jacobson et al. (1985) found that consumption of PCB-contaminated fish by mothers and serum cord levels of PCBs were predictors of poor visual recognition memory and fixation to novelty in infants. The doses of PCBs consumed by the mothers cannot be determined in these studies.

Collins and Capen (1980a) fed diets containing Aroclor 1254 at 0, 50, or 500 ppm to female rats during gestation and lactation. Significantly ($P < 0.001$) reduced litter size occurred at 500 ppm. At both 50 and 500 ppm, the neonates and weanlings had ultrastructural

lesions in the thyroid follicular cells and reduced serum levels of thyroid hormone. Thus, 50 ppm is the LOAEL for fetotoxicity due to oral exposure in rats. Assuming that a rat consumes a daily amount of food equal to 5% of its body weight (EPA 1986a), 50 ppm is equivalent to 2.5 mg/kg/day. The LOAEL is indicated on Figs. 2.2 and 2.5 for developmental toxicity in rats.

Gestational exposure to Aroclor 1254 by gavage produced fetotoxic effects in rabbits exposed on days 1-28 at doses >12.5 mg/kg/day but not <10 mg/kg/day (Villeneuve et al. 1971). The dose of 10 mg/kg/day, therefore, represents a NOAEL for developmental effects in rabbits (see Figs. 2.2 and 2.5, acute exposure). The dose of 12.5 mg/kg/day represents a FEL for developmental effects in rabbits because it produced fetal deaths.

Haake et al. (1987) reported that treatment of pregnant C57BL/6 mice with Aroclor 1254 by gavage at 244 mg/kg on day 9 of gestation did not result in any fetuses with cleft palate. This dose is plotted on Figs. 2.2 and 2.5 as a NOAEL for developmental toxicity in mice.

Monkeys that were fed diets containing 1.0 ppm of Aroclor 1016 for approximately 7 months prior to mating and during pregnancy delivered infants with reduced birth weights, but this affect did not occur at 0.25 ppm (Barsotti and Van Miller 1984). Assuming that a monkey consumes a daily amount of food equal to 4.2% of its body weight, the daily dosages in the 1.0 ppm (LOAEL) and 0.25 ppm (NOAEL) groups were 0.04 and 0.0105 mg/kg/day, respectively. The NOAEL serves as the basis for the minimal risk level for intermediate and chronic oral exposure as derived by EPA (1987a). Fetal mortality, a frank affect, occurred at >2.5-ppm (0.1-mg/kg/day) dietary concentrations of Aroclor 1248 in other studies with monkeys (Allen and Barsotti 1976; Allen et al. 1979, 1980).

Reproductive toxicity. There are no studies regarding reproductive effects of PCBs in humans. Diets that provided >2 ppm of Aroclor 1254 for 4 months prior to mating and during gestation were lethal to fetuses and caused reproductive failure in mink (Aulerich and Ringer 1977, Bleavins et al. 1980). Assuming that mink consume 150 g of feed per day and weigh 800 g (Bleavins et al. 1980), then the 2-ppm FEL provided 0.38 mg/kg/day (see Figs. 2.2 and 2.5).

Reduced litter sizes occurred at Aroclor 1254 dietary concentrations of >20 ppm but not <5 ppm in one- and two-generation reproduction studies with rats (Linder et al. 1974). The dietary concentrations of 5 ppm (NOAEL) and 20 ppm (FEL) provided 0.25 and 1 mg/kg/day, respectively, if rat food consumption is assumed to be 5% of body weight per day (EPA 1986a). These levels are plotted on Figs. 2.2 and 2.5 for reproductive effects of intermediate oral exposure in rats.

Genotoxicity. The PCBs have produced generally negative results in in vivo and in vitro genotoxicity tests (Sect. 4.3.5 on genotoxicity in toxicological data section).

Carcinogenicity. EPA (1987a) used the Norback and Weltman (1985) study as the basis for a quantitative carcinogenicity risk assessment for PCBs. The dietary level of 100 ppm Aroclor 1260 was converted to an intake of 5 mg/kg/day by assuming that a rat consumes food equal to 5% of its body weight per day. This dosage was converted to a TWA dosage of

3.45 mg/kg/day (see Fig. 2.5) to reflect the fact that rats received 100 ppm for 16 months, 50 ppm for 8 months, and 0 ppm for the last 5 months. The rat dosage was converted to an equivalent human dose of 0.59 mg/kg/day on the basis of relative body surface areas. Incidences of trabecular carcinomas, adenocarcinomas, and neoplastic nodules in the liver were combined to produce total incidences of 45/47 in treated females and 1/49 in controls. Using these data, EPA (1987a) calculated a human q_1^* of 7.7 $(mg/kg/day)^{-1}$. Dosages corresponding to risk levels of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} are 1.3×10^{-5}, 1.3×10^{-6}, 1.3×10^{-7}, and 1.3×10^{-8} mg/kg/day, respectively. The 10^{-4} to 10^{-6} risk levels are indicated on Fig. 2.5.

2.2.1.3 Dermal

Occupational exposure to PCBs is considered to be by the inhalation route in this profile, since air levels are commonly monitored in the workplace setting. It is clear, however, that under occupational conditions dermal exposure would also occur. This was recognized by ACGIH (1986) when a skin notation was placed with the TLV. Dermal adsorption and exposure can occur from contact of the skin with the vapors of PCB as well as actual dermal contact with the compound or with contact with dust or surfaces to which the PCBs are absorbed. Although it is realized that dermal exposure may be a major route of exposure in the occupational setting, quantitation of the relative contribution to body burden of absorbed PCBs from the inhalation and dermal routes is not possible.

Lethality and decreased longevity. Human data are not available. Median lethal doses for single dermal applications of PCBs to rabbits ranged from >1269 mg/kg for Aroclors 1242 and 1248 to <3169 mg/kg for Aroclor 1221 (Fishbein 1974). As only ranges of median lethal doses were reported, the lowest dose (1269 mg/kg) is indicated on Figs. 2.3 and 2.6.

Systemic target organ toxicity. Occupational exposure to PCBs involves dermal contact, but, for reasons discussed previously, occupational exposure data were discussed under inhalation exposure.

Dermal application of Aroclor 1260 to rabbits on 5 days/week at a dose of 118 mg/day for 38 days (27 total applications) produced degenerative lesions of the liver and kidneys, increased fecal porphyrin elimination, and hyperplasia and hyperkeratosis of the follicular and epidermal epithelium (Vos and Beems 1971). As body weight appeared to be approximately 2.7 kg (Vos and Beems 1971), the FEL of 118 mg/day is equal to a dose of 43.7 mg/kg/day (see Figs. 2.3 and 2.6).

Developmental and reproductive toxicity. Pertinent data regarding developmental and reproductive effects of dermal exposure to PCBs were not located in the available literature.

Genotoxicity. The PCBs have produced generally negative results in in vivo and in vitro genotoxicity tests (Sect. 4.3.5 on genotoxicity in toxicological data section).

Carcinogenicity. Occupational exposure to PCBs, which involves inhalation as well as dermal exposure, provides inadequate evidence of carcinogenicity in humans (Sect. 4.3.6 on carcinogenicity in

toxicological data section). Aroclor 1254 has shown weak tumor initiator but not promoter activity in two-stage carcinogenesis studies with mouse skin. Dermal studies of PCBs as whole carcinogens have not been conducted in animals (Sect. 4.3.6.3 on carcinogenicity of dermal exposure in toxicological data section).

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

2.2.2.1 Exposure

PCBs are pervasive environmental contaminants that are found in body tissues and fluids of the general population, including adipose tissue, blood, and breast milk.

In the National Human Adipose Tissue Survey (NHATS), 46 composite adipose tissue samples collected during surgical procedures or during autopsies during fiscal year 82 were analyzed for organochlorine compounds (EPA 1986b). Of the 46 samples, 83% contained PCBs as follows: 22% contained trichlorobiphenyl, 53% contained tetrachlorobiphenyl, 73% contained pentachlorobiphenyl, 73% contained hexachlorobiphenyl, 53% contained heptachlorobiphenyl, 40% contained octachlorobiphenyl, 13% contained nonachlorobiphenyl, and 7% contained decachlorobiphenyl. EPA (1985a) performed a statistical analysis for baseline estimates and time trends for PCBs in human adipose tissue in the NHATS for 1970-1983. The findings indicated that 5.5% of the population had a PCB level >1 ppm compared with the historic percentage of 28.9%. The percentage of people who had >1 ppm PCB levels increased with age and was greater in males than in females, but there was no significant race difference. Historically, the Northeast Census Region has had the greatest percentage of people with levels >1 ppm, but, in recent years, the difference between the northeast and other regions no longer exists. Although 100% of the samples contained detectable levels of PCBs, there was a steady decrease over time in the percentage of people with >1 ppm.

Anderson (1985) discussed the use of adipose tissue biopsy in assessing human exposure to PCBs. Because adipose tissue is the primary storage site of PCBs, adipose tissue samples have been the preferred biological specimen. Analysis of PCBs in adipose tissue provides a direct measure of body burden, but has disadvantages over analysis of serum levels because collection of samples is invasive and time-consuming. Based on data that adipose tissue levels of PBBs (polybrominated biphenyls) and DDT are directly correlated with serum levels of PBB and DDT, it can be predicted that PCB adipose levels will also correlate with serum levels. Anderson (1985) recommended that whenever an adipose tissue sample is obtained at biopsy, a paired serum sample should be collected and the two tissues be analyzed for PCBs. Once the correlation is characterized, blood samples may become the preferred choice for monitoring, unless identification of low exposures is required.

Wolff (1985) reported data on blood levels of PCBs in workers in relation to exposure levels (Table 2.1) and blood and adipose tissue

Table 2.1. PCB levels in blood of exposed workers (Aroclors 1016, 1242, 1248)

Air levels (mg/m^3)	Blood levels (ng/mL)		
	Mean	High	*N*
0.3–2	1060	3500	19 "Inside"[a]
	440	1400	14 "Outside"[a]
0.05–0.275	130	407	60
0–0.26	355	3330	26 High exposed
	149	1500	55 Low exposed
	89	370	140 Never exposed
0.1–1	118	2530	110 High exposed
	48	604	180 Other

[a]Workers who were exposed inside or outside the impregnation room.

Source: Wolff 1985.

MONS 027297

levels of PCBs in workers in relation to duration of employment (Table 2.2). Generally, higher exposure levels result in higher blood and adipose tissue levels of PCBs, but because PCBs accumulate in the body, exposure duration is at least as important as exposure level.

Kreiss (1985) reviewed available data, including unpublished Centers for Disease Control (CDC) data, for serum PCB concentrations in U.S. populations without occupational exposures for 1968-1983. Mean serum levels were usually between 4 and 8 ng/mL, with 95% of the individuals having concentrations <20 ng/mL (Table 2.3). Cross-sectional data concerning PCB levels in a representative sample of the U.S. population are not available because the various groups were monitored during investigations of pesticide residues, food chain contamination, hazardous waste sites, and occupational exposure in which a nonexposed control group was necessary. Subpopulations consuming fish taken from contaminated waters have mean serum PCB levels that are several times higher than those in other general population groups and comparable to those usually associated with occupational exposure (Table 2.4). Interpretation of the data in Tables 2.3 and 2.4 is complicated by differences in analytical methodology and methods of population selection and data reporting (Kreiss 1985).

PCB levels in adipose tissue and in human milk fat are 100 to 200 times higher than serum levels (Kimbrough 1987a). PCB concentrations averaged 1.5 ppm in the breast milk of 1057 women in Michigan (Wickizer et al. 1981). These levels are relatively high and apparently due to consumption of contaminated fish.

2.2.2.2 Effects

Several studies of general population subjects attempted to correlate serum PCB levels with health indices. Baker et al. (1980) found that plasma triglyceride levels increased significantly with serum PCB concentrations in residents of Bloomington, Indiana, including workers occupationally exposed to PCBs. Chloracne or systemic symptoms of PCB toxicity were not noted, and there were no significant correlations between PCB levels and hematologic, hepatic, or renal function indices. Kreiss et al. (1981) reported that serum PCB levels were positively associated with serum cholesterol levels, gamma-glutamyl transpeptidase (GGTP) levels, and measured blood pressure in residents of Triana, Alabama, that were exposed via consumption of contaminated fish. The associations in the above studies were independent of predictors of PCB levels such as age, sex, and/or consumption of alcohol and fish. Although PCBs may be related to elevated blood pressure (Kreiss et al. 1981), the effect has not been validated and has uncertain relevance to PCB exposure because the fish also contained high concentrations of DDT residues.

Steinberg et al. (1986) determined that five serum analytes (β-glucuronidase, 5'-nucleotidase, triglycerides, cholesterol, and total bilirubin) correlated positively and significantly with log concentrations of serum total PCBs in residents who lived or worked in the vicinity of an electrical manufacturing plant. Aroclor 1260 was significantly and positively correlated with several of the analytes,

Table 2.2. PCB blood levels (Aroclor 1254) and duration of exposure

Mean duration of employment (years)	Mean blood concentration (ng/mL)	N	Mean adipose concentration (μg/g)	N
12 ± 6	238	80		
16 ± 8	24[a]	258	17	53
	6[b]	32	4	8
17	33[c]	86	5.6	36
3.8	14[d]	15	1.4	5
4.3	12[e]	19	1.3	9

[a]Persons with more than 5 years employment; geometric means; geometric mean of 53 plasma samples which matched the adipose samples was 54 ng/mL.
[b]Persons with less than 5 years employment; geometric means.
[c]Persons exposed.
[d]Persons nominally exposed.
[e]Nonexposed.
Source: Wolff 1985.

MONS 027299

Table 2.3. Serum PCB concentrations in U.S. populations without occupational exposure to PCBs and in subpopulations consuming fish from PCB-contaminated waters

Area and sampling method	Number of subjects	Year	PCB level, ng/mL: Arithmetic mean	Geometric mean, median[a]	Arithmetic standard deviation	95% confidence interval	Range	References
Populations without occupational exposure, 1968–1983								
Charleston County, S.C., volunteers	616	1968	4.9	–	–	–	0–29	Finklea et al. 1972
Lake Michigan random non-fish eaters	29	1973	17.3	15[a]	–	–	<5–41	Humphrey 1983a
Bloomington, Ind., volunteers and controls	110	1977	18.0	–	10.8	17–21	6–79	Baker et al. 1980
Michigan PBB cohort	1631	1978–79	7.7	6.4	–	–	<1–57	Kreiss et al. 1982
Billings, Mont., random packinghouse workers	17	1979	7.5	5.0	6.0	4–11	2–30	Drotman et al. 1981
Franklin, Idaho, volunteers	105	1979	–	–	–	–	<5	Drotman et al. 1981
Random unexposed workers	19	1979	12	–	–	–	10–27	Chase et al. 1982
Newton, Kans., volunteers	7	1979	4.9	4.2	3.1	2–8	2–11	Vernon et al. 1981
Lake Michigan random non-fish eaters	418	1980	–	6.6[a]	–	–	<3–60	Humphrey 1983a
Canton, Mass., volunteers	10	1980	7.1	5.2	5.2	3–11	1–18	Condon 1983
Old Forge, Pa., volunteers	138	1981	3.6	–	–	–	<3–43	Reid and Fox 1982

MONS 027300

Table 2-3 (continued)

Area and sampling method	Number of subjects	Year	PCB level, ng/mL: Arithmetic mean	Geometric mean, median[a]	Arithmetic standard deviation	95% confidence interval	Range	References
Jefferson, Ohio, volunteers	59	1983	5.8	4.4	6.5	4-8	1-45	Wolff 1983
Fairmont, W. Va., volunteers	40	1983	6.7	5.0	5.3	5-8	1-23	Wolff 1983
Norwood, Mass., volunteers	990	1983	4.9	4.2	3.5	4-6	2-30	Condon 1983
Populations without occupational exposures consuming PCB-contaminated fish								
Lake Michigan volunteer sportfishers	90	1973	72.7	56[a]	–	–	25-366	Humphrey 1983b
Triana, Ala., volunteers	458	1979	22.2	17.2	22.3	20-24	3-158	Kreiss et al. 1981
Lake Michigan volunteer sportfishers	572	1980	–	21.4[a]	–	–	<3-203	Humphrey 1983b
New Bedford, Mass., volunteers	11	1981	31.4	23.6	29.3	13-50	5-101	Condon 1983

[a]Median.
Source: Kreiss 1985.

MONS 027301

Table 2.4. Serum PCB concentrations in populations with occupational exposure

Facility	PCB levels, ng/mL: Number of subjects	Arithmetic mean	Geometric mean	95% confidence interval	Range	References
Railway car maintenance	86	33.4	–	–	10–312	Chase et al. 1982
Capacitor plant	34	394[a]	–	234–554	trace–1700	Ouw et al. 1976
Capacitor plant	290	124[b] 48[c]	67[b] 21[c]	98–150[b] 38–58[c]	6–2530[b] 1–546[b]	Fischbein et al. 1979 Wolff et al. 1982a
Capacitor plant	80	342[a]	–	–	41–1319	Marconi et al. 1981a
Capacitor plant	221	–	119[b] 25.3[c]	–	1–3330[b] 1–250[c]	Smith et al. 1982
Public utility	14	–	24[b] 24[c]	15–39[b] 16–35[c]	5–52[b] 7–24[c]	Smith et al. 1982
Private utility	25	–	22[b] 29[c]	17–25[b] 20–43[c]	9–48[b] 7–250[c]	Smith et al. 1982

[a]Blood level.
[b]Lower PCB homologs.
[c]Higher PCB homologs.
Source: Kreiss 1985.

MONS 027302

but Aroclor 1242 was correlated significantly and negatively only with HDL-cholesterol.

Umbilical cord serum levels of PCBs have been correlated with reduced birth weight and size, shorter gestation, and neonatal behavioral effects in a few reports (Fein 1984; Fein et al. 1984; Jacobson et al. 1984a, 1985; Rogan et al. 1986). Although increased levels of PCBs in cord blood may be predictors of these kinds of effects, the effects are not well validated. Cord serum levels associated with these effects are reported in Sect. 4.3.3 (developmental toxicity in toxicological data section).

Workers with occupational exposure to PCBs (see Table 2.4) have also been evaluated for subclinical associations with serum lipids and other health indices (Kreiss 1985). Significant correlations between plasma PCB and serum triglycerides (Chase et al. 1982), plasma triglycerides (Smith et al. 1982), SGOT (Chase et al. 1982, Smith et al. 1982, Fischbein et al. 1979), SGTP (Ouw et al. 1976), and GGTP (Smith et al. 1982, Maroni et al. 1981a, Fischbein 1985) have been reported. Measures of liver enzyme induction (e.g., GGTP) are not commonly associated with PCB levels, and possible hepatocellular damage (as indicated by SGOT, SGTP) has been demonstrated only in occupationally exposed groups with higher ranges of PCB levels (Kreiss 1985).

Maroni et al. (1981a) examined the health condition and PCB blood levels of 80 electrical workers exposed to PCBs (42% mean chlorine content) for many years. They found that hepatic involvement was associated with blood concentration of trichlorobiphenyls (Student t test, $P < 0.001$), but the association with pentachlorobiphenyls was not as great ($P < 0.01$). Individuals with abnormal liver findings had average blood trichlorobiphenyl concentrations of 215 μg/kg (range 77-407 μg/kg), while workers without abnormal liver findings had average concentrations of 92 μg/kg (range 13-345 μg/kg). The abnormal liver findings include hepatomegaly and altered liver enzyme levels, with well-defined liver failure noted in a few cases. The authors suggested that trichlorobiphenyls may reflect current PCB exposure levels more closely than pentachlorobiphenyls.

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

The purpose of this subsection is to summarize available data that suggest that levels of PCBs found in environmental media (primarily soil, drinking water, and food) are associated with significant human exposure and/or effects. Schwartz et al. (1983) found a significant positive correlation ($P < 0.001$) between fish consumption measures and PCB levels in maternal serum and milk. The specific PCBs present were not correlated with the various Aroclor mixtures. From their data, Schwartz et al. (1983) determined that serum PCB levels increase by 0.15 ng/mL and milk levels increase by 0.12 ng/g for every 0.45 kg of PCB-contaminated fish consumed. The rate of fish consumption was not stated. Drotman et al. (1983) found a positive correlation between the PCB concentration in human breast milk and the number of contaminated eggs consumed by lactating women.

2.2.3.2 Human exposure potential

The purpose of this subsection is to discuss the chemical-specific issues involved in human exposure of PCBs from water, soil, and food. Experimental monitoring data have shown that PCB concentrations are higher in sediment and suspended matter than in the associated water column, and this is in agreement with the high soil adsorption constants for PCBs. The partitioning between suspended matter and water will be isomer specific and should correlate with the octanol/water partition coefficient of individual isomers. Thus, lower chlorinated PCBs should have a greater tendency to partition to the water than higher chlorinated PCBs. This implies that human exposure to the higher chlorinated isomers from whole water (water + sediment) will be greater than from settled water. Therefore, the human exposure potential to higher chlorinated PCBs from contaminated waters will increase as exposure to sediment and suspended matter increases. The exposure of lower chlorinated PCBs from drinking water from contaminated sources should remain about the same whether the water is filtered or not.

In general, PCBs are strongly adsorbed in most soils; therefore, leaching will not generally occur. This implies that the exposure will be greatest at the point of initial adsorption. In many instances, this may be at or near the soil surface. The principal route of human exposure to PCBs from a spill in soil at a restricted outdoor site is through inhalation of air (EPA 1987b). Soil ingestion and dermal contact with soil would not be expected to be significant routes of exposure at a limited access site. Nonetheless, ingestion is considered the primary route of exposure from spills at a nonrestricted residential site, although it is anticipated that some exposure would occur through inhalation also. Although dermal exposure can occur at soil sites where access is possible, it is expected that the PCBs will adsorb to the soil particles, reducing the rate of dermal absorption. The bioavailability of PCBs through inhalation may be higher for the lower chlorinated congeners since their tendency to volatilize from soil is greater than the tendency of the higher chlorinated congeners to volatilize.

2.3 ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List.

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This section identifies data gaps in current knowledge relevant to developing levels of significant exposure for PCBs. Such gaps are identified for certain health effects end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for PCBs, and for other areas such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the adequacy of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for PCBs will be developed by ATSDR, NTP, and EPA in the future.

2.3.2 Adequacy of Database for Health Effect End Points

2.3.2.1 Introduction and graphic summary

The adequacy of the PCB database for health effect end points in humans and animals is depicted on bar graphs in Figs. 2.7 and 2.8, respectively.

The bars of full height indicate that there are "adequate" data to meet at least one of the following conditions:

1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from no effect levels (NOAELs) to levels that cause effects (LOAELs or FELs).
2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA and the International Agency for Research on Cancer (IARC) (qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).
3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species, and the data are sufficient to derive a cancer potency factor.
4. There are studies which show that the chemical does not cause this health effect via this exposure route.

Bars of half height indicate that "some" data for the end point exist but do not meet any of the criteria for "adequate" data.

2.3.2.2 Descriptions of highlights of graphs

Data concerning effects of PCBs in humans that are useful for quantitative risk assessment are not available. The available data pertain primarily to intermediate- or chronic-duration occupational exposures in which the exposures are inadequately monitored and do not

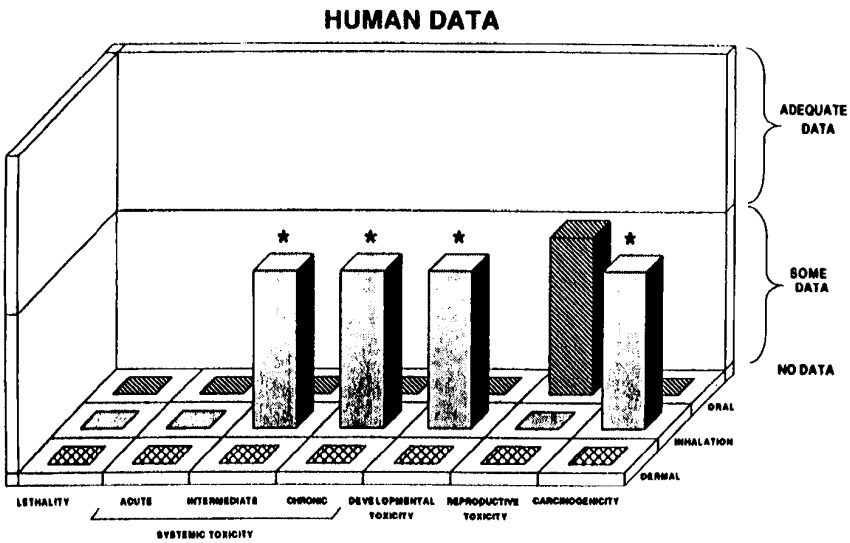


Fig. 2.7. Adequacy of the database on health effects of PCBs (human data).

MONS 027306

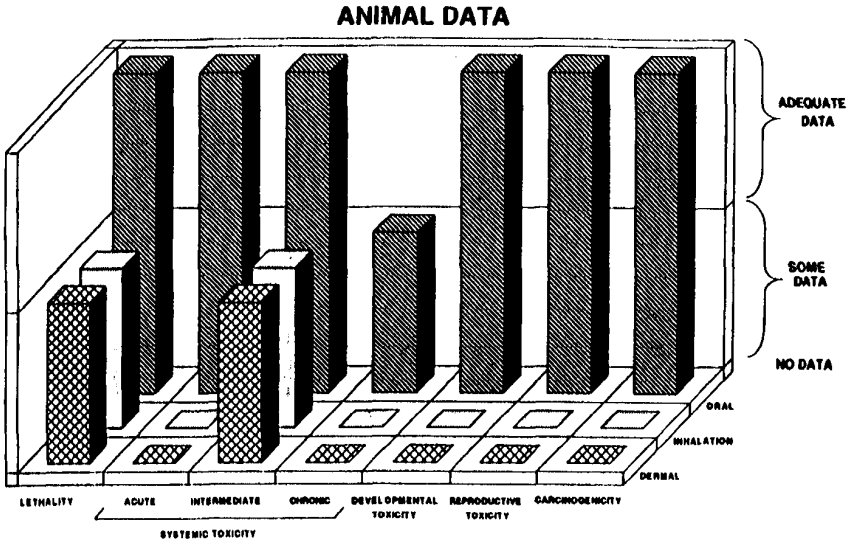


Fig. 2.8. Adequacy of the database on health effects of PCBs (animal data).

MONS 027307

correlate with duration and intensity of exposure. Occupational exposures to PCBs involve significant dermal exposure, but, as discussed previously, occupational concentrations are expressed milligrams per cubic meter of air (mg/m^3). For this reason, occupational exposure data were discussed under inhalation exposure. Children born to mothers who consumed PCB-contaminated fish had some developmental effects, but the effects cannot be directly attributed to PCBs; therefore, the bar for developmental effects due to oral exposure indicates that there are some data.

The toxicity and carcinogenicity of the PCBs in animals by the oral route are reasonably well characterized. Determination of toxicity effect levels for chronic oral exposure is precluded by occurrence of proliferative/neoplastic alterations. Effects of acute oral, inhalation, and dermal exposures to the PCBs in animals have not been extensively investigated because concern for effects in humans is centered on intermediate/chronic-duration oral exposures.

2.3.2.3 Summary of relevant ongoing research

J.L. Jacobson of Wayne State University is conducting a study sponsored by the National Institute of Environmental Health Sciences to evaluate the impact of PCBs on physical, cognitive, and neurological development in early childhood. The children, examined at age 4, were exposed to moderate levels of PCBs, or maternal serum PCB levels were high near the time of their birth (NTIS 1987).

W.J. Rogan of the National Institute of Environmental Health Sciences is conducting a follow-up study of children exposed to PCBs through breast milk. The children under study are a cohort of 856 North Carolina children exposed to relatively low levels of PCBs and a cohort of 108 children from Taiwan exposed to relatively high levels of PCBs (NTIS 1987).

2.3.3 Adequacy of the Database for Other Information Needed for Risk Assessment

2.3.3.1 Pharmacokinetics and mechanism of action

Quantitative data concerning the pharmacokinetics of PCBs following inhalation and dermal exposure are lacking. Such data could greatly assist efforts to evaluate health effects resulting from inhalation and dermal exposure to PCBs. Further studies should be conducted concerning the distribution of PCBs, especially regarding the distribution of PCBs in the plasma compared to adipose tissue.

Ongoing studies concerning pharmacokinetics and mechanisms of action were not located.

2.3.3.2 Monitoring of human biological samples

PCBs can be measured in serum, adipose tissue, and milk. These measurements can indicate elevated exposure but do not provide information concerning the route of exposure. Although biological monitoring is useful for documenting exposures, it cannot be used for predicting health effects.

MONS 027308

Biological monitoring methods indicate body burden of PCBs that have accumulated over a lifetime. Adequate methods are not available to distinguish exposure routes, short or intermittent exposures, or low-level exposures due to the bioaccumulation and slow excretion of PCBs.

Several studies concerning monitoring of biological samples are ongoing. The Massachusetts Department of Health (population survey in New Bedford, Massachusetts) and the Indiana State Department of Health (population survey in Monroe County, Indiana) are conducting studies that will provide information on PCB body burden levels in conjunction with selected health outcomes. Several smaller studies are being conducted by the CDC.

2.3.3.3 Environmental considerations

Methodology of sufficient sensitivity and specificity to measure PCBs in the environment exists.

The bioavailability of PCBs from environmental media appears to be fairly well understood.

There appears to be a fairly good understanding of the environmental fate and transport of PCBs; however, more experimental data are required to understand the potential importance of photolysis in degrading the more highly chlorinated PCBs, which are more persistent in the environment. In addition, a better understanding of the environmental cycling of PCBs is needed to assess future exposure from current environmental sinks such as PCBs adsorbed to sediments.

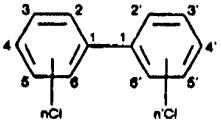
No studies were found that involve the environmental interaction of PCBs with other pollutants.

There are no known ongoing experimental studies pertaining to the environmental fate of PCBs, which would help to fill the data gaps as mentioned above.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of the Aroclors are listed in Table 3.1. Aroclors are mixtures of chlorinated biphenyls. The general chemical structure of chlorinated biphenyls is as follows:



(where n and n' may vary from 0 to 5).

The numbering system for the biphenyl structure is also shown above.

Aroclor products are identified by a four-digit numbering code in which the first two digits (12) indicate that the parent molecule is biphenyl and the last two digits indicate the chlorine content by weight. Thus, Aroclor 1242 is a chlorinated biphenyl mixture with an average chlorine content of 42%. The exception to this designation method is Aroclor 1016, which retained the 1016 designation by which it was known during development (Misurs et al. 1976). Aroclor 1016 is a mixture that contains primarily mono-, di-, and trichloro isomers and has an average chlorine percentage (41.5%) that is very similar to Aroclor 1242.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Selected physical and chemical properties of the Aroclors are presented in Table 3.2. Table 3.3 identifies the approximate molecular composition of the Aroclors.

Data pertaining to the pyrolysis of PCBs which results in the formation of polychlorinated dibenzofurans (PCDFs) have been reviewed (EPA 1987a). Several studies involving pyrolysis of specific PCB isomers have found that the pyrolysis products include PCDFs, chlorinated benzenes, naphthalenes, phenyl ethynes, biphenylenes, and hydroxy PCBs. There appear to be four major paths for production of PCDFs from PCBs: (1) loss of two ortho chlorines, (2) loss of ortho hydrogen as well as chlorine, (3) loss of an ortho hydrogen as well as chlorine but involving a shift of chlorine from the 2- to the 3-position, and (4) loss of two ortho hydrogens (EPA 1987a). The formation of PCDFs from the pyrolysis of PCBs occurred when an electrical transformer in an office

MONS 027310

building in Binghamton, New York, accidentally caught fire on February 5, 1981 (Schecter and Tiernan 1985, Tiernan et al. 1985).

MONS 027311

Table 3.1. Chemical identity of the Arochors

	Chemical name[a]							
	Arochor 1016	Arochor 1221	Arochor 1232	Arochor 1242	Arochor 1248	Arochor 1254	Arochor 1260	References
Synonyms	PCB-1016 Polychlorinated biphenyl with 41.5% Cl	PCB-1221 Polychlorinated biphenyl with 21% Cl	PCB-1232 Polychlorinated biphenyl with 32% Cl	PCB-1242 Polychlorinated biphenyl with 41.5% Cl	PCB-1248 Polychlorinated biphenyl with 48% Cl	PCB-1254 Polychlorinated biphenyl with 54% Cl	PCB-1260 Polychlorinated biphenyl with 60% Cl Chlorodiphenyl (60% Cl)	SANSS 1987
Trade names	b	b	b	b	b	b	b	
Chemical formula	See Table 3.3	See Table 3.3	See Table 3.3	See Table 3.3	See Table 3.3	See Table 3.3	See Table 3.3	
Wiswesser line notation[c]	NA	NA	NA	NA	NA	NA	NA	
Chemical structure	See text	See text	See text	See text	See text	See text	See text	
Identification Nos.								
CAS Registry No.	12674-11-2	11104-28-2	11141-16-5	53469-21-9	12672-29-6	11097-69-1	11096-82-5	SANSS 1987
NIOSH RTECS No.	TQ1351000	TQ1352000	TQ1354000	TQ1356000	TQ1358000	TQ1360000	TQ1362000	SANSS 1987
EPA Hazardous Waste No.[d]	3502	3502	3502	3502	3502	3502	3502	EPA 1980a
OHM-TADS No.	8500400	8500401	8500402	8500403	8500404	8500405	8500406	EPA-NIH 1987
DOT/UN/NA/IMCO Shipping No.	UN2315	UN2315	UN2315	UN2315	UN2315	UN2315	UN2315	Chemline 1987
STCC No.	4961666	4961666	4961666	4961666	4961666	4961666	4961666	Stone 1981
Hazardous Substances Data Bank No.	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	1822	HSDB 1987
National Cancer Institute No.	Unknown	Unknown	Unknown	Unknown	Unknown	C02664	Unknown	NCI 1978

[a] These are the current chemical names as indexed by the Chemical Abstracts Service (CAS).
[b] Arochor is the trade name for chlorinated biphenyls used by Monsanto.
[c] Wiswesser line notations are not applicable for mixtures.
[d] Designation prior to May 19, 1980.

MONS 027312

Table 3.2. Physical and chemical properties of PCBs

	Aroclor designation							
	1016	1221	1232	1242	1248	1254	1260	References
Molecular weight[a]	257.9	200.7	232.2	266.5	299.5	328.4	375.7	Hutzinger et al. 1974
Color	Clear	Clear	Clear	Clear	Clear	Light yellow	Light yellow	Monsanto 1974
Physical state	Oil	Oil	Oil	Oil	Oil	Viscous liquid	Sticky resin	Monsanto 1974
Odor	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	
Melting point, °C	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	
Boiling point, °C (distillation range)	325–356	275–320	290–325	325–366	340–375	365–390	385–420	Monsanto 1974
Autoignition temperature	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	
Solubility								
Water, mg/L	0.42	0.59 (24°C)	Unknown	0.24 0.34 0.10 (24°C)	0.054 0.06 (24°C)	0.012 0.057 (24°C)	0.0027	Monsanto 1974, Parsons et al. 1978, Hollifield 1979
Organic solvents	Very soluble	Very soluble	Very soluble	Very soluble	Very soluble	Very soluble	Very soluble	EPA 1985a
Density, g/cm³ at 25°C	1.33	1.15	1.24	1.35	1.41	1.50	1.58	Monsanto 1974
Partition coefficient Log octanol-water[b]	5.6	4.7	5.1	5.6	6.2	6.5	6.8	b
Vapor pressure, mm Hg at 25°C	4×10^{-4}	6.7×10^{-5}	4.06×10^{-5}	4.06×10^{-4}	4.94×10^{-4}	7.71×10^{-5}	4.05×10^{-5}	Monsanto 1974, Callahan et al. 1979
Henry's law constant, atm-m³/mol at 25°C[c]	2.9×10^{-4}	3.5×10^{-3}	Unknown	5.2×10^{-4}	2.8×10^{-3}	2.0×10^{-3}	4.6×10^{-3}	c
Refractive index	1.6215–1.6235 (25°C)	1.617–1618 (20°C)	Unknown	1.627–1.629 (20°C)	Unknown	1.6375–1.6415 (25°C)	Unknown	IARC 1978

MONS 027313

Table 3.2 (continued)

	Aroclor designation							
	1016	1221	1232	1242	1248	1254	1260	References
Flash point, °C (Cleveland open cup)	Unknown	176	238	None	None	None	None	Hubbard 1964
Flammability limits	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	
Conversion factors								
Air (25°C)[d]	1 mg/m³ = 0.093 ppm	1 mg/m³ = 0.12 ppm	1 mg/m³ = 0.105 ppm	1 mg/m³ = 0.092 ppm	1 mg/m³ = 0.08 ppm	1 mg/m³ = 0.075 ppm	1 mg/m³ = 0.065 ppm	
Water	ppm (w/v) = mg/L = μg/mL	Same	Same	Same	Same	Same	Same	

[a]Average mass from Table 3.3.

[b]These log K_{ow} values represent an average value for the major components of the individual Aroclor. Experimental values for the individual components were obtained from Hansch and Leo 1985.

[c]These Henry's law constants were estimated by dividing the vapor pressure by the water solubility. The first water solubility given in this table was used for the calculation. The resulting estimated Henry's law constant is only an average for the entire mixture; the individual chlorobiphenyl isomers may vary significantly from the average. Burkhard et al. (1985) estimated the following Henry's law constants (atm-m³/mol) for various Aroclors at 25°C: 1221 (2.28×10^{-4}), 1242 (3.43×10^{-4}), 1248 (6.4×10^{-4}), 1254 (2.83×10^{-4}), 1260 (4.15×10^{-4}).

[d]These air conversion factors were calculated by using the average molecular mass as presented under molecular weight.

MONS 027314

Table 3.3. Approximate molecular composition of PCBs (percent)

Empirical formula	Aroclor designation						
	1016	1221	1232	1242	1248	1254	1260
$C_{12}H_{10}$	<0.1	11	<0.1	<0.1	ND[a]	<0.1	ND
$C_{12}H_9Cl$	1	51	31	1	ND	<0.1	ND
$C_{12}H_8Cl_2$	20	32	24	16	2	0.5	ND
$C_{12}H_7Cl_3$	57	4	28	49	18	1	ND
$C_{12}H_6Cl_4$	21	2	12	25	40	21	1
$C_{12}H_5Cl_5$	1	<0.5	4	8	36	48	12
$C_{12}H_4Cl_6$	<0.1	ND	<0.1	1	4	23	38
$C_{12}H_3Cl_7$	ND	ND	ND	<0.1	ND	6	41
$C_{12}H_2Cl_8$	ND	ND	ND	ND	ND	ND	8
$C_{12}H_1Cl_9$	ND	ND	ND	ND	ND	ND	ND
Average molecular mass	257.9	200.7	232.2	266.5	299.5	328.4	375.7

[a]ND = none detected.
Source: Hutzinger et al. 1974.

MONS 027315

4. TOXICOLOGICAL DATA

4.1 OVERVIEW

Evaluation of the toxicokinetics and toxicity of PCBs is complicated by the fact that PCBs are mixtures of a variety of different congeners and impurities, each with its own characteristics. Impurities include the highly toxic PCDFs. Aroclor PCBs are the subject of this profile, but toxicokinetics studies often examined specific congeners, and many toxicity studies used mixtures of PCBs other than Aroclors, particularly Kanaclors. Kaneclors are similar to Aroclors but are produced in Japan rather than the United States and differ in method of production, chlorine content, and PCDF contamination. The reported range of PCDFs in Kaneclors and Aroclors is 5 to 20 ppm and 0 to 2 ppm, respectively. Reference to Kaneclors is made occasionally to support statements about Aroclors because effects produced by Aroclors and Kaneclors are similar. Kaneclor toxicity data are not considered in detail because of the aforementioned differences in composition and because reported lowest effect levels are lower for Aroclors than Kaneclors.

The general population is exposed to PCBs primarily by the oral route (through food, particularly fish). Inhalation and dermal exposure are the primary routes of occupational exposures, but the relative contribution of these routes is unknown.

Studies of the absorption of PCBs following oral exposure indicate that gastrointestinal absorption of most isomers is >90%. The limited data concerning the absorption of PCBs following inhalation and dermal exposure indicate that PCBs can be absorbed via these exposure routes.

Distribution of ingested or injected Aroclors follows a biphasic pattern. During the first day following dosing, the PCBs distribute to the liver and muscle tissue. The compounds are then redistributed to fat, skin, and other fat-containing organs. Heavily chlorinated congeners redistribute to adipose tissue to a greater extent than the less chlorinated congeners, although the type of chlorine substitution is also a factor.

A number of studies indicate that PCBs can cross the placenta and locate in the fetus. PCBs also concentrate in milk. Higher PCB levels may reach the offspring through nursing than through placental transfer.

The metabolism of PCBs is dependent on the number and position of chlorine atoms, with lesser chlorinated isomers metabolized more readily than more chlorinated isomers. PCB metabolites tend to be 3- or 4-hydroxy compounds produced via an arene oxide intermediate. The presence of vicinal unsubstituted carbon atoms at the 3-4 positions may be helpful but not essential to this process.

MONS 027316

PCBs that are metabolized with more difficulty tend to be excreted almost exclusively through the biliary route, while the metabolites of mono-, di-, and trichlorinated isomers are also eliminated through the urine. Urinary metabolites are in the form of conjugates, including glucuronides and sulfates. Glutathione conjugates have also been identified.

Higher chlorinated PCBs tend to persist in the body longer than lower chlorinated PCBs. For example, biological half-lives in the rat range from 1.15 days for 2,2'-dichlorobiphenyl to 460 days for 2,2',4,4'-hexachlorobiphenyl.

Aroclors appear to have a low order of acute lethality. Data for non-Aroclor PCB mixtures and specific PCB isomers suggest that mice and guinea pigs are more sensitive than rats. Aroclors are lethal at much lower total doses when administered subchronically or chronically than acutely, indicating that PCBs bioaccumulate to concentrations that are toxic.

Animal studies have shown that the liver and cutaneous tissues are the major target organs for Aroclors. Aroclors have also been shown to produce stomach and thyroid alterations, immunosuppressive effects, and porphyria in animals. Animals are sensitive to repeated exposures to Aroclors as a result of rapid bioaccumulation to toxic levels. Monkeys are particularly sensitive to the toxic effects of Aroclors. Gross toxic effects other than reversible skin lesions have not been associated with Aroclor exposure (occupational) in humans. Biochemical effects, however, such as increased liver enzyme levels, have been associated with Aroclor exposure in workers and in the general population.

More serious health effects were observed in humans who consumed rice oil that had been contaminated with Kaneclors in Japan ("Yusho" incident) and Taiwan ("Yu Cheng" incident). Although there is an historical linkage between Yusho and PCBs and some regulatory documents ascribe health effects from these incidents to PCBs, effects from the incidents are not reviewed in this report because exposure was to Kaneclors and because the effects cannot be attributed specifically to the Kaneclors. The Kaneclors were heated in thermal heat exchangers before the rice oil contamination and during cooking and contained relatively high concentrations of PCDFs and polychlorinated quaterphenyl contaminants. There appears to be general agreement that the PCDF contaminants, particularly the more potent isomers, contributed significantly to the health effects observed in the Yusho and Yu Cheng patients. Please refer to Kuratsune and Shapiro (1984) for a more complete discussion of this topic.

Aroclors appear to be fetotoxic but not teratogenic in various species of animals, including rats, mice, rabbits, and monkeys, but the possibility that contaminants (e.g., PCDFs) may be responsible for the effects should be recognized. Effects such as decreased birth weight, shortened gestation age, and neonatal behavioral alterations have been associated with PCB exposure in humans.

Oral exposure to Aroclors produced deleterious effects on reproduction in monkeys, mink, and, at higher doses, rodents.

PCBs have produced generally negative results in in vitro and in vivo mutagenicity assays.

Feeding studies in laboratory animals demonstrated the carcinogenicity of several PCB mixtures, but it is not clear which components of the mixture or metabolites are actually carcinogenic. The liver is the primary target of PCB carcinogenicity.

4.2 TOXICOKINETICS

4.2.1 Absorption

4.2.1.1 Inhalation

Human. Inhalation exposure and dermal exposure are the primary routes of occupational exposure to PCBs, but the relative contribution of each route has not been discerned (Wolff 1985).

Animal. Six rats were exposed to an aerosol of a PCB mixture (Pydraul A200, 42% chlorine) at a concentration of 30 g/m^3 (0.5 to 3 μm particles) for 30 min (Benthe et al. 1972). PCB concentrations in the liver 15 min after cessation of exposure were >50% of the maximum concentration attained after 2 h (70 $\mu g/g$ tissue). These data indicate that the PCBs were readily absorbed.

4.2.1.2 Oral

Human. The general population is exposed to PCBs primarily by the oral route (primarily by consumption of contaminated fish). Schwartz et al. (1983) found elevated levels of PCBs in the serum and breast milk of women who ate PCB-contaminated fish from Lake Michigan. Humphrey (1976) reported blood levels of PCBs in people who consumed contaminated sport fish from Lake Michigan in 1973. Annual consumption of ≥24 lb resulted in a mean blood level of 0.073 ppm, while annual consumption of ≤6 lb resulted in a mean blood level of 0.020 ppm. Blood levels of PCBs in persons who ate no fish averaged 0.017 ppm. These studies indicate that PCBs are absorbed by the gastrointestinal tract, but do not provide information regarding the extent of absorption.

Animal. Drill et al. (1981) and EPA (1985a) reviewed a number of animal studies indicating that PCBs, including Aroclors, are absorbed readily from the gastrointestinal tract following oral administration. Albro and Fishbein (1972) examined the absorption of 19 PCB congeners and unchlorinated biphenyl in rats treated by gavage at doses of 5, 50, or 100 mg/kg. Determination of PCBs in feces collected for 4 days indicated that absorption of all congeners was >90%. Using rhesus monkeys, Allen et al. (1974a,b) determined over 2-week periods that >90% of a single oral dose of 1.5 or 3.0 g/kg Aroclor 1248 was absorbed. Bleavins et al. (1984) determined over 5 weeks that European ferrets absorbed 85.4% of a single dose of [^{14}C]-labeled Aroclor 1254 (0.05 mg) given in food.

In contrast to the above studies, Norback et al. (1978) claimed that 59.3 to 87% of a single oral dose of 2,4,5,2',4',6'-HCB passed unabsorbed through the intestine of monkeys during the first week after dosing. It was unclear why relatively little of this isomer was

absorbed. There are no data on the effect of the environmental matrix or vehicle on the bioavailability of specific PCBs and PCB mixtures. Studies with 2,3,7,8-TCDD indicate that the vehicle may play a significant role in the relative bioavailability of 2,3,7,8-TCDD and related compounds (e.g., PCBs) (EPA 1985b).

4.2.1.3 Dermal

Human. In a study of occupational exposure of electrical workers to PCBs (Pyralen 3010 and Apirolio, 42% chlorine content), Maroni et al. (1981b) concluded that absorption of PCBs occurred mainly through the skin. Quantitive data were not available.

Animal. Miller (1944) reported the deaths of guinea pigs and rabbits treated dermally with a mixture of PCBs containing approximately 42% chlorine. The guinea pigs were treated with 34.5 mg/day for 11 days, while rabbits were treated with 86 mg every other day for 7 doses or 172 mg every other day for 8 doses. Lesions observed in guinea pigs and rabbits included fatty degeneration and centrolobular hepatocellular atrophy of the liver.

Using tritium-labeled PCBs (40% chlorine), Nishizumi (1976) found evidence for dermal absorption of PCBs in rats via follicular diffusion. Quantitative data were not provided.

4.2.2 Distribution

4.2.2.1 Inhalation

Human. Wolff et al. (1982b) examined the relative concentrations of PCB congeners in plasma and adipose tissue of 26 persons occupationally exposed to PCBs (20 to 54% chlorine). Exposure was not discussed, but it probably included both inhalation and dermal exposure. The results indicated that PCB congeners with chlorines in both 4-positions were the major components in plasma and adipose tissue. PCBs with unsubstituted 3,4- positions on at least one ring were observed at lower concentrations in plasma and adipose. The adipose-plasma partition ratio calculated for Aroclor 1248 residues was 185, while the partition ratio for Aroclor 1254 residues was 190. In a more recent study of 173 workers from the same population, adipose-plasma partition ratios of 210, 190, and 200 were determined for Aroclors 1242, 1254, and 1260, respectively (Brown and Lawton 1984).

Animal. Maximum PCB concentrations in the liver and brain of rats occurred 2 and 24 h, respectively, after a single 30-min exposure to 30 g/m^3 of Pydraul A200 aerosol (42% chlorine) (Benthe et al. 1972). Concentrations in these tissues subsequently declined, while adipose concentrations reached a maximum after 48 h.

4.2.2.2 Oral

Human. A number of studies reviewed by EPA (1987a) indicate that PCBs concentrate in human breast milk. Exposures in these studies were most likely oral, but may have included both inhalation and dermal exposure. Wolff (1983) reported the half-life of PCBs (percentage chlorine in compounds not stated) in breast milk at 5 to 8 months and found that the concentration of PCBs in breast milk was 4 to 10 times

that in maternal blood. Similar results were reported by Jacobson et al. (1984b).

Ando et al. (1985) examined the PCB concentration in maternal blood and milk and the placenta of six Japanese women. They found that the congeners present were more typical of Kanechlor 500 than Kanechlors 300, 400, or 600. The results indicated that as the chlorine content of the PCB congeners increased, the correlation between the placental content of congeners and maternal blood and milk also increased.

PCBs were detected in the umbilical tissues, umbilical blood, amniotic fluid, and baby's blood from a woman who was occupationally exposed to Kanechlors 300 and 500 in a capacitor factory (Yakushiji et al. 1978). PCB levels in these tissues and fluids were considerably less than in the mother's blood. Maternal serum concentrations of PCBs were also higher than cord serum concentrations in women who resided in western Michigan (Jacobson et al. 1984b) and upstate New York (Bush et al. 1984) (i.e., in regions with easy access to fish from the Great Lakes).

Kraul and Karlog (1976) determined PCB levels in abdominal fat, brain, and liver from necropsies completed in 1972 and 1973 in Copenhagen, Denmark. The ratios of PCB levels were reported as 1:3.5:81 for brain:liver:fat, indicating that adipose was the site of greatest bioaccumulation of the tissues studied.

Animal. Following absorption, PCBs, including Aroclors, are distributed in a biphasic manner. The compounds rapidly (minutes to hours) clear from the blood and accumulate in the liver and muscles (Drill et al. 1981). PCBs may be translocated from the liver to adipose tissue for storage or be metabolized in the liver, with metabolites excreted in the urine or bile.

Muehleback and Bickel (1981) treated rats by gavage with a single dose of 0.6 or 3.6 mg/kg [^{14}C]-2,4,5,2',4',5'-hexachlorobiphenyl. The rats were examined 1 h, 24 h, 6 weeks, 20 weeks, or 40 weeks after dosing. The results showed the highest levels of PCBs in muscle, liver, fat, and skin early in the study. By the end of the study, the highest PCB levels were found in adipose tissue followed by skin, muscle, and liver. During the 40-week study period, only 16% of the total dose was excreted.

Gage and Holm (1976) determined concentrations in abdominal fat of mice 7 and 21 days after the mice were dosed by gavage with a single dose (13-165 μg/mouse) of 1 of 14 PCB congeners. Relatively low levels (<10 ng/g/μg dose) were found at 7 days for 4,4'-, 3,2',4',6'-, and 2,3,4,2',4',6'- isomers, with relatively high levels (≥100 ng/g/μg dose) for 2,4,5,2',4',5-, 4,2'4'6'-, and 2,4,2'4'- PCBs.

Kurachi and Mio (1983a) exposed mice to Kanechlor-400 at 100 mg/kg in the diet for 5 to 20 days. Analysis of tissues at the end of the feeding period indicated high levels of PCBs in the gonads. High levels of PCBs were also found in skin, adipose tissue, adrenals, and kidneys. A second group of mice were kept on the PCB diet for 20 days in a rotation cage to cause fatigue. Mobilization of fat deposits was observed with liver PCB levels in fatigued mice 10 times greater than in mice fed the same diets but allowed to rest.

A number of animal studies have demonstrated that PCB mixtures and specific congeners and isomers can cross the placental barrier and accumulate in fetuses (EPA 1987e). High levels of PCBs also accumulate in the mammary gland where they are secreted in the fat portion of the milk. Masuda et al. (1979) fed PCBs to pregnant mice through the first 18 days of gestation and found the highest levels of serum PCBs in offspring 1 to 2 weeks old. In studies in which monkeys were exposed prior to and during gestation, signs of PCB-induced intoxication in nursing but not newborn offspring were observed (Allen and Barsotti 1976, Iatopoulos et al. 1978). Results such as these have led some investigators to conclude that transfer through nursing may account for higher exposure of young than does placental transfer. This conclusion may be inappropriate, as it is often based on the fact that the absolute quantity of PCB residues is substantially higher in breast milk than cord serum; relative to fetal body weight, even low-level prenatal exposure can cause substantial concentrations (Jacobson et al. 1985).

Groups of 24 rhesus monkeys were maintained on diets that provided Aroclor 1016 at doses of 0, 4.5, or 18.1 mg/kg/day throughout gestation and a 4-month gestation period (Barsotti and Van Miller 1984). At birth, the concentrations of the PCBs in the skin of infants were similar to concentrations in the subcutaneous fat of the mothers. At weaning, the PCB content in the mesenteric fat of the infants was 4 to 7 times greater than in the subcutaneous fat of the mothers. Gas chromatographic patterns showed that the adult adipose tissue did not include the total spectrum of peaks observed in the Aroclor 1016 standard, that all of the peaks observed in the standard occurred in the neonate skin, and that the peaks in the mesenteric fat at weaning and 4 months after weaning were qualitatively similar to those in the adult adipose tissue. These data suggested an inability of the fetus to metabolize and excrete certain congeners that are more readily metabolized and eliminated by adults and older infants.

Bleavins et al. (1984) fed female European ferrets a single dose of [^{14}C]-labeled Aroclor 1254 in the diet (0.05 mg) early (day 14) or late (day 35) in gestation and determined the placental transfer of PCBs. They found that placental transfer to the kits was 0.01% (per kit) of the maternal dose when dams were exposed early in gestation and 0.04% (per kit) when dams were exposed late in gestation. Placental transfer of PCBs was considerably less than mammary transfer, with the ratio of placental to mammary transfer at 1 week of lactation 1:15 and 1:7 for offspring of dams dosed early and late in gestation, respectively.

4.2.2.3 Dermal

Data concerning the distribution of Aroclors following dermal exposure of humans or animals were not located. Because PCBs are lipophilic, the compounds should concentrate in adipose tissue regardless of the route of exposure.

4.2.3 Metabolism

4.2.3.1 Human

2,2',4,4',5,5'-Hexa-CB was the PCB congener found in the highest concentration in human adipose tissue, while 2,2',4,4',6,6'-hexa-CB was

not detected (Jensen and Sundstrom 1974). As both of these compounds are found in commercial PCB mixtures and in the environment, the presence of the 2,2',4,4',5,5'-hexa-CB congener in adipose tissue appears to be related to resistance to metabolism (EPA 1987a). That this congener is not metabolized or is minimally metabolized is also indicated by the finding that the blood concentration of this congener decreased only 10% over 300 to 500 days (Chen et al. 1982) and by the results of in vitro metabolism studies with human liver microsomes (Schneilman et al. 1983, 1984).

There were lower concentrations of PCBs with unsubstituted 3,4-positions on at least one of the phenyl rings than PCBs with substitutions in the 2,4- or 3,4- positions on both rings in the blood and adipose tissue from capacitor-manufacturing facility workers (Wolff et al. 1982a).

4.2.3.2 Animal

The metabolism of PCBs has been investigated in numerous studies with animals and reviewed by EPA (1987a) and Drill et al. (1981). A variety of substrates have been tested, and the PCBs were usually administered by the oral or parenteral routes. General findings of these studies reported by EPA (1987a) are presented below.

Phenolic products are the major PCB metabolites although sulfur-containing metabolites (e.g., methylsulfones), trans-dihydrodiols, polyhydroxylated PCBs, and methyl ether derivatives have also been identified. Although the effects of chlorine substitution patterns on sites of oxidation have not been studied systematically, EPA (1987a) suggests the following:

1. Hydroxylation is favored at the para position in the least chlorinated phenyl ring unless this site is sterically hindered (i.e., 3,5-dichloro substitution).

2. In the lower chlorinated biphenyls the para position of both biphenyl rings and carbon atoms that are para to the chloro substituent are all readily hydroxylated (Sparling et al. 1980).

3. The availability of two vicinal unsubstituted carbon atoms (particularly C5 and C4 in the biphenyl nucleus) also facilitates oxidative metabolism of the PCB substrate but is not a necessary requirement for metabolism.

4. As the rate of chlorination increases on both phenyl rings the rate of metabolism decreases.

5. The metabolism of specific PCB isomers by different species can result in considerable variations in metabolite distribution.

MONS 027322

The occurrence of *trans*-dihydrodiol metabolites suggests that metabolism of PCBs proceeds through formation of arene oxide intermediates (EPA 1987a). Arene oxides are potential electrophiles that have been implicated in cellular necrosis, mutagenicity, and carcinogenicity. The toxicological significance of PCB metabolism is unknown, but most studies suggest that the parent hydrocarbon initiates most of the common toxic responses by initial binding to the cytosolic receptor protein (EPA 1987a). The role of metabolism in the genotoxicity of PCBs has not been delineated.

PCB metabolites are usually more polar than the parent compounds and conjugated with glucuronides or sulfates prior to elimination. Rats and mice that were exposed to di-, tetra-, or penta- CBs by intraperitoneal injection or diet eliminated metabolites of glutathione conjugates and other sulfur-containing compounds (Kurachi 1983, Kurechi and Mio 1983b).

4.2.4 Excretion

4.2.4.1 Inhalation

Data concerning the excretion of PCBs in humans and animals following inhalation exposure were not available.

4.2.4.2 Oral

The excretion of PCBs is to a large extent dependent on the metabolism of PCBs to more polar compounds (EPA 1987a). At equilibrium, the elimination of PCBs from all tissues will be dependent on the structure-dependent metabolism rates of the individual PCB congeners. For example, biological half-lives in the rat range from 1.15 days for 2,2'-dichlorobiphenyl to approximately 460 days for 2,2',4,4',5,5'-hexachlorobiphenyl (Tanabe et al. 1981, Wyss et al. 1986). Metabolites of the more highly chlorinated congeners are eliminated primarily via the feces (Goto et al. 1974).

Human. Chen et al. (1982) report on the determination of PCBs in the blood of humans in Taiwan after they consumed rice-bran oil contaminated with Kanechlor 500 and PCDFs. Blood samples from 17 patients were examined, with 2 to 3 samples taken from each patient 2 to 17 months apart. The results indicated that the tetra- and some penta-isomers tend to be eliminated more rapidly than other penta-, hexa-, and hepta- isomers. Half-lives for the 2,4,5,2',4'- and 2,3,4,3',4'-penta-isomers in blood were determined to be 9.8 and 8.7 months, respectively. The data also indicated that two adjacent unsubstituted carbon atoms at the meta-para positions facilitated metabolism and subsequent elimination from the blood.

Animal. Hashimoto et al. (1976) examined the excretion of [^{14}C] PCB compounds given to rats by gavage at a total dose of 6.35 to 7.85 mg/kg over a period of 5 to 50 days. The PCBs studied were predominantly tetra- and hexa-chlorinated isomers. The results indicated that 1.9 to 4.9% of the dose of tetra-PCBs was excreted in the urine, with higher amounts excreted in rats treated for longer periods. In rats treated with hexa-PCBs, only 0.3% of the dose was excreted in the urine. About 47 to 68% of the dose of both tetra- and hexa- isomers was excreted in the feces.

Mizutani et al. (1977) studied the elimination of tetra-CB isomers in mice fed diets containing a single isomer at 10 ppm for 20 days. Biological half-lives for the individual isomers were 0.9, 9.2, 3.4, 0.9, and 2.1 days for 2,3,2',3'-; 2,4,2',4'-; 2,5,2',5'-; 3,4,3'4'-; and 3,5,3',5'-, respectively. The authors were not able to relate the difference in rates of elimination to chlorine substitution patterns.

In a study of the influence of molecular structure on the excretion of 14 PCB congeners in mice, Gage and Holm (1976) found that the 4,4'-; 3,3',4',6'-; 2,3,2',4',6'-; and 2,3,4,2',4',5'- isomers were eliminated most rapidly. These compounds had at least one pair of ortho-meta vicinal carbon atoms unsubstituted, a configuration thought to be important for rapid metabolism and excretion. The most slowly eliminated compounds were 2,4,5,2',4',5'- and 2,3,4,2',4',5'-hexa- isomers.

Felt et al. (1977) examined the elimination of [^{14}C]-2,5,4'-tri-CB in rhesus monkeys. The monkeys were fed 550 mg of the compound in fruit daily for 84 days. On the basis of total excreted and recovered radioactivity, the half-life of 2,5,4'-tri-CB was found to be 4.5 to 4.8 days.

Bleavins et al. (1984) examined the excretion of PCBs in female European ferrets given a single dose of 0.05 mg [^{14}C]-labeled Aroclor 1254 in food. The results showed that urinary excretion accounted for ≤1/10 of the quantity of PCB that was eliminated in the feces. Excretion of PCBs was highest during the first week following dosing, when 22.1 and 1.8% of the absorbed dose was excreted in the feces and urine, respectively.

4.2.4.3 Dermal

Data concerning the excretion of PCBs by humans or animals following dermal exposure were not located.

4.2.4.4 Parenteral Routes

Human. No data were located in the available literature.

Animal Studies. Injection studies indicate that PCBs can be excreted unmetabolized into the gastrointestinal tract. Yoshimura and Yamamoto (1975) recovered unmodified tetra-CB from the duodenal contents of rats injected intravenously with tetra-CB. Daily excretion for 4 days ranged from 0.5 to 0.8% of the total dose per day. Goto et al. (1974) found that 4.7 to 23.2% of injected PCBs were excreted unchanged into the gastrointestinal tract by 10 days postdosing, with the excretion of a penta- isomer greater than the excretion of di-, tri-, or tetra-isomers.

4.3 TOXICITY

Evaluation of the toxicity of Aroclors and other commercial PCB mixtures is complicated by numerous factors, including isomer and congener composition, differences in species susceptibility, quantitatively inconsistent data, and varying degree of contamination with toxic contaminants such as chlorinated dibenzofurans. Because of these factors and a lack or paucity of data for some of the Aroclors (most of the studies were conducted with the higher chlorinated

MONS 027324

Aroclors), it is assumed that effects resulting from exposure to a specific Aroclor are representative of effects which may be produced by the other Aroclors. In the following sections, data delineating the threshold region of the most toxic Aroclor for specific end points are presented. Although the relative contribution of the inhalation and dermal routes in occupational exposures is unknown, health effects data for exposed workers are discussed in the inhalation subsections.

4.3.1 Lethality and Decreased Longevity

4.3.1.1 Inhalation

Human. Pertinent data were not located in the available literature.

Animal. Inhalation LC50s of Aroclor were not located in the available literature. Roznaova (1963) reported that all four rats exposed to Solvol (a European PCB mixture) at concentrations of 10 g/m^3 for 3 h became comatose and died, while 11 similar exposures at 0.5 g/m^3 resulted in only one death. Liver and renal damage was noted along with congestion in the heart and spleen. Insufficient detail was available to determine how the atmosphere was generated or what methods were used to verify the concentration. Treatment-related mortality was not observed in groups of 9 to 10 rats, 6 to 10 mice, 3 to 4 rabbits, 4 to 6 guinea pigs or 1 cat that were exposed 7 h/day, 5 days/week to vapor concentrations of 8.6 mg/m^3 (0.83 ppm) Aroclor 1242 for 24 days, 5.4 mg/m^3 (0.41 ppm) Aroclor 1254 for 121 days, 6.83 mg/m^3 (0.66 ppm) Aroclor 1242 for 120 days, 1.5 mg/m^3 (0.11 ppm) Aroclor 1254 for 213 days, or 1.9 mg/m^3 (0.18 ppm) Aroclor 1242 for 214 days (Treon et al. 1956). It was necessary to heat the Aroclors to 55 to 138°C to attain the above concentrations, and 8.6 mg/m^3 Aroclor 1242 was "approaching saturation" concentration. These concentrations may be low as the technique used to estimate them was invalidated. Possible contamination by PCDF was not reported.

4.3.1.2 Oral

Human. Pertinent data were not located in the available literature.

Animal. Acute oral LD50 values for the PCBs covered by this profile (Aroclors 1254, 1221, 1260, 1232, 1242, and 1248) are presented in Table 4.1. No values for Aroclor 1016 were found in the available literature. The lowest oral LD50 in rats was 1.01 g/kg for Aroclor 1254 as reported by Garthoff et al. (1981). In mink, the lowest LD50 was between 0.75 and 1.0 g/kg for Aroclor 1221 as reported by Aulerich and Ringer (1977). As seen from the data of Grant and Phillips (1974) and Linder et al. (1974), immature rats appear to be more sensitive than adult rats. The full range of LD50 values for all PCBs is greater, with the lowest value of 0.5 g/kg for hexachlorobiphenyl in guinea pigs (McConnell and McKinney 1978) and the highest value of 11.3 g/kg reported for Aroclor 1262 in the rat (Fishbain et al. 1974).

In mice maintained on diets that provided 1000 ppm Aroclor 1254 for 14 days, 3/5 died of unspecified causes by day 15 (Sanders et al. 1974). All mice treated at 4000 ppm died within 7 days after the onset of

Table 4.1. Acute oral LD_{50}s of Aroclors

Aroclor	Species/strain	Sex/age	LD_{50} (g/kg)	References
1254	Rat/Wistar	M/30 days	1.3	Grant and Phillips 1974
		F/30 days	1.4	
		M/60 days	1.4	
		F/60 days	1.4	
		M/120 days	2.0	
		F/120 days	2.5	
	Rat/Sherman	M/weanling	1.295	Linder et al. 1974
		NR*/adult	4-10	
	Rat/Osborne-Mendel	M/adult	1.01 (single dose)	Garthoff et al. 1981
			1.53 (5 doses over 2½ weeks)	
			1.99 (5 doses, 1 day/week)	
	Mink/pastel	NR/NR	4	Aulerich and Ringer 1977
1221	Rat/NR	NR/NR	3.98	Fishbein 1974
	Rat/Sherman	F/NR	4.0	Nelson et al. 1972
	Mink/pastel	NR/NR	>0.75 to <1.0	Aulerich and Ringer 1977
1260	Rat/Sherman	NR/adult	4-10	Linder et al. 1974
		M/weanling	1.315	
1232	Rat/NR	NR/NR	4.47	Fishbein 1974
1242	Rat/Sprague-Dawley	M/adult	4.25	Bruckner et al. 1973
	Rat/NR	NR/NR	8.65	Fishbein 1974
	Mink/pastel	NR/NR	>3	Aulerich and Ringer 1977
1248	Rat/NR	NR/NR	11	Fishbein 1974

*NR = not reported.

MONS 027326

treatment. No deaths occurred in five mice that were similarly treated with 250 ppm.

For intermediate-exposure durations, the LC_{50} for Aroclor 1254 fed to mink in the diet for 28 days ranged from 79 to 84 ppm and 47 to 58 ppm after a 7-day withdrawal period (Hornshew et al. 1986). In mink fed Aroclor 1254 for 9 months, the LC_{50} was 6.65 ppm (Ringer et al. 1981). Death generally was due to nonspecific hemorrhagic lesions.

Groups of 24 male rats that were fed diets containing 0, 25, 50, or 100 ppm Aroclor 1254 for 104 to 105 weeks experienced dose-related decreased survival (92, 83, 58, and 46%, respectively) (NCI 1978). The cause of death was not specified but may have been related to development of nodular hyperplasia in the liver. There was no effect on survival of female rats similarly treated. There was no attempt to identify or quantitate impurities.

4.3.1.3 Dermal

Human. Pertinent data were not located in the available literature.

Animal. Median lethal doses for single application of Aroclors to the skin of rabbits ranged from >1269 mg/kg for Aroclors 1242 and 1248 in 50% corn oil to <3169 mg/kg for undiluted Aroclor 1221 as reported by Nelson et al. (1972) and summarized by Fishbein (1974) (Table 4.2).

4.3.2 Systemic/Target Organ Toxicity

4.3.2.1 Liver

Inhalation, human. Epidemiological studies and clinical surveys indicate that occupational exposure to Aroclors can produce alterations in liver enzymes (e.g., SGOT, GGTP) that are inconsistent and not clearly associated with clinically detectable liver disease (Ouw et al. 1976; Alvares et al. 1977; Fischbein et al. 1979, 1985; Baker et al. 1980; Smith et al. 1981a,b,c; Brown and Jones 1981; Fischbein 1985; Emmett 1985; Lawton et al. 1985; Drill et al. 1981; Kriess 1985). Asymptomatic hepatomegaly was reported in one study (Maroni et al. 1981a). The subjects of these studies were primarily involved in electrical equipment (e.g., capacitors, transformers) manufacturing and repair, and many had measurable and often high serum levels of PCBs.

Monitoring data were reported only in some of the studies and do not adequately characterize exposure levels because of limitations and dissimilarities in sampling methods, durations, and locations, changes in workplace ventilation and Aroclor formulations during the exposure period, wide ranges in concentrations within and between studies without indications of average levels, emphasis on correlating effects with serum PCB concentrations rather than air concentrations of PCBs, and unknown contribution of dermal exposure to total exposure. It appears, however, that air concentrations of Aroclors were often <1 mg/m^3. In one study that reported comprehensive monitoring data, capacitor-manufacturing plant workers were exposed primarily to Aroclors 1242 and 1254 at 8-h average time-weighted concentrations that ranged from 0.07 to 11.0 mg/m^3 (Fischbein et al. 1979). Approximately 40% (131) of the workers in this study were employed for ≥20 years. There was a

MONS 027327

Table 4.2. Acute dermal LD_{50} values of Aroclors in rabbits

Aroclor	Vehicle	LD_{50} (mg/kg)
1221	Undiluted	>2000 <3469
1232	Undiluted	>1260 <2000
1242	Undiluted	>794 <1269
1248	Undiluted	>794 <1269
1260	50% corn oil	>1260 <2000

Source: Fishbein 1974.

MONS 027328

correlation between SGOT and serum PCB levels. Alvares et al. (1977) found that the mean antipyrine half-life was significantly lower in five workers exposed to Aroclor 1016 (10.8 h) than in controls (15.6 h).

Inhalation, animal. Reversible degenerative lesions of the liver were observed in rats, mice, rabbits, cats, and guinea pigs exposed to 1.5 mg/m^3 (0.11 ppm) Aroclor 1254 vapor 7 h/day, 5 days/week for a 213-day period (Treon et al. 1956). Exposure to Aroclor 1242 for 7 h/day, 5 days/week at 1.9 mg/m^3 (0.18 ppm) for 214 days or 8.6 mg/m^3 (0.83 ppm) for 24 days did not produce histological effects in the liver or other viscera. It was necessary to heat the Aroclors to attain the concentrations used in this study.

Oral, human. Serum PCB levels were positively associated with increased GGTP levels and blood pressure in Triana, Alabama, residents that were exposed to contaminated fish (Kreiss et al. 1981). The significance of these effects is uncertain as the fish also contained high concentrations of DDT. Hepatic function indices were not affected in residents of Bloomington, Indiana, that had PCBs in their serum (Baker et al. 1980).

Oral, animal. Carter (1985) exposed groups of 12 male Charles River rats to 0, 4, 8, or 16 ppm of Aroclor 1254 in the diet for 4 days and found that relative liver weights were increased at ≥8 ppm.

Litterst et al. (1972) exposed groups of six male Osborne-Mendel rats to Aroclors 1260, 1254, 1248, or 1242 in the diet at concentrations of 0, 0.5, 5.0, or 500 ppm for 4 weeks. Increased microsomal nitroreductase and demethylase activities occurred at ≥0.5 ppm, increased pentobarbital hydroxylation and relative liver weight occurred at ≥50 ppm, and increased liver triglycerides occurred at 500 ppm.

Dietary exposure to 5 or 25 ppm Aroclor 1242 for 2, 4, or 6 months produced increased hepatic microsomal hydroxylase activity and histochemically discernible lipid content of hepatocytes in groups of six male Sprague-Dawley rats (Bruckner et al. 1974). Increased relative liver weight was observed at 25 ppm at 4 and 6 months and at 5 ppm at 4 months.

Frank histological effects in the liver (e.g., fatty degeneration) occurred in rats exposed to ≥20 ppm Aroclor 1254 or 1260 for 28 days (Chu et al. 1977), rats exposed to ≥20 ppm Aroclor 1254 or 1260 for 8 months (Kimbrough et al. 1972), and mice exposed to 37.5 ppm but not 3.75 ppm Aroclor 1254 for 6 months (Koller 1977).

In a study in which 4 male and 18 female rhesus monkeys were fed diets containing Aroclor 1248, Barsotti et al. (1976) conducted autopsies on one female monkey that died after being fed 2.5 ppm of Aroclor 1248 for 173 days and on one female monkey that died after being fed 5.0 ppm of Aroclor 1248 for 310 days. Hepatic effects in both monkeys included focal areas of necrosis, enlarged hepatocytes, and lipid droplets. Although only one animal per dose was examined, these effects must be regarded as treatment-related because of the characteristic nature of the hepatic response. Also, similar effects on the liver were observed in an earlier study by Allen (1975) in which the animals received Aroclor 1248 in the diet at levels of 100 and 300 ppm for 2 or 3 months.

Chronic dietary studies were conducted with rats exposed to 25 to 100 ppm Aroclor 1254 for 2 years (NCI 1978, Morgan et al. 1981, Ward 1985), 100 ppm Aroclor 1260 for 16 months followed by 50 ppm for 8 months, and then no treatment for 5 months (Norback and Weltman 1985) or 100 ppm Aroclor 1260 for 21 months (Kimbrough et al. 1975). Treatment-related nonproliferative liver lesions or nonproliferative liver lesions that did not progress to neoplasms after 1 year were not described in these studies.

The effects of chlorination and chemical composition of PCBs with regard to the dose effects relation of liver toxicity after subchronic exposure are indicated by the data of Biocca et al. (1981). In this study, hepatotoxic effects were observed in mice after 5 weeks of maintenance on diets containing 0.3 ppm of 3,4,5-symmetrical hexachlorobiphenyl, while similar effects were observed only after 30 ppm of 2,4,5-symmetrical hexachlorobiphenyl and 100 ppm of 2,4,6-symmetrical hexachlorobiphenyl, and no effects were noted after 300 ppm of 2,3,6-symmetrical hexachlorobiphenyl. Similar dependence of liver toxicity on the chemical composition of the PCB mixture would be anticipated following chronic exposure in mice and other species.

None of the above studies reported possible contamination of the Aroclor with PCDF.

Dermal. Aroclor 1260 in isopropanol vehicle was applied to the shaved backs of groups of four female New Zealand rabbits daily 5 days/week at a dose of 118 mg/day for 38 days (Vos and Beems 1971) or 120 mg/day for 28 days (Vos and Notenboom-Ram 1972). Histological alterations were produced in the livers, including centrolobular degeneration and liver cell atrophy, focal hyalin degeneration of the cytoplasm of the hepatocyte, enlarged nuclei, and loss of glycogen. Aroclor 1260 used in these experiments was reported to be free of PCDF contamination.

General discussion. The liver is the organ most often implicated in the toxicity of Aroclors in animals. Hepatotoxicity is suggested in occupationally exposed humans (EPA 1987a, Drill et al. 1981). Hepatic effects have been observed in numerous studies with exposed rats, mice, guinea pigs, rabbits, dogs, and monkeys, but rats have been tested most extensively. The effects appear to be reversible at low doses, are similar among species, and include enzyme induction, liver enlargement, fat deposition, and necrosis. Enzyme induction is the most sensitive indicator of hepatic effects, but few studies were designed to define minimum effective doses of Aroclors. The liver enlargement is associated with hepatocyte enlargement and an increase in smooth endoplasmic reticulum and/or increased enzymatic activity. Proliferative lesions in the liver have been attributed to Aroclor treatment (Sect. 4.3.6 on carcinogenicity in this section). The hepatic effects of Aroclors in animals appear to be typical of chlorinated hydrocarbons.

Histologically documented liver damage is a consistent finding among PCB-exposed animals. That hepatic alterations have been inconsistently observed in humans may be related to the fact that many of the studies (particularly the earlier ones) did not account for confounding variables, such as alcohol consumption, exposure to additional chemicals, or previous medical histories, or may be an

artifact of the relative insensitivity of the standard biochemical tests of liver damage (e.g., SGOT) as compared with biopsy evaluation (Letz 1983, Drill et al. 1981). Drill et al. (1981) concluded that SGOT and/or GGPT appear to be the most sensitive indicators of PCB exposure in humans, and that changes in liver enzymes may occur at levels below those at which chloracne occur. Abnormal liver function and some hepatomegaly have been documented in Yusho and Yu Cheng patients, but PCDFs, polychlorinated quaterphenyls, and perhaps other contaminants (e.g., chlorinated diphenyl ethers) are significant etiologic factors (Fischbein 1985).

Aroclors are commonly used to induce hepatic enzymes in animal studies with other chemicals. Exposures in these studies are not representative of realistic human exposures, as large doses are usually given by intraperitoneal injection or gavage to obtain maximal enzyme induction. Induction of enzymes by PCBs occurs in both the cytochrome P-450 and P-448 systems, has been observed in humans, and is not restricted to the liver (Letz 1983). Implications of enzyme induction for human health include the occurrence of disease secondary to the increased metabolism of endogenous or exogenous substances, and the interference with medical therapy due to increased metabolism of administered drugs (Letz 1983).

Safe et al. (1985) reviewed data concerning the mechanism of PCB induction of liver microsomal enzymes. The activity of individual PCBs depends on their structure. The most active congeners are those substituted at both para and at two or more meta positions and include 3,4,4',5-tetra-, 3,3',4,4'-tetra-, 3,3',4,4',5-penta-, and 3,3',4,4',5,5'-hexachlorobiphenyl. The coplanar PCBs induce rat liver microsomal aryl hydrocarbon hydroxylase and cytochromes P-450a, P-450c, and P-450d, thus resembling 3-methylcholanthrene and 2,3,7,8-TCDD in their mode of microsomal enzyme induction. Mono-ortho- and di-orthochloro analogs of coplanar PCBs exhibit a mixed type of enzyme induction similar to Aroclor 1254. These PCBs induce aryl hydrocarbon hydroxylase, dimethylaminoantipyrine, *N*-demethylase, and cytochromes P-450a through P-450e. Results of quantitative structure-activity relationships showed a correlation between aryl hydrocarbon hydroxylase induction activity and binding affinity for the 2,3,7,8-TCDD cytosolic receptor protein, with the order of activity as follows: coplanar PCBs > 3,4,4',5-tetrachlorobiphenyl ≈ mono-ortho coplanar PCBs > diortho coplanar PCBs. Support for the receptor-mediated mechanism of action was found when the coplanar and mono-ortho coplanar PCBs were administered to C57BL/6J and DBA/2J mice. C57BL/6J mice contain much higher concentrations of the Ah receptor than do DBA/2J mice. The PCBs induced aryl hydrocarbon hydroxylase in the responsive C57BL/6J mice but not in the unresponsive DBA/2J mice.

4.3.2.2 Cutaneous tissues

Inhalation, human. Effects such as chloracne, skin rashes, and burning eyes and skin have been associated with occupational exposure to Aroclors (Meigs et al. 1954; Ouw et al. 1976; Fischbein et al. 1979; 1982, 1985; Baker et al. 1980; Smith et al. 1981a,b,c; NIOSH 1977a; EPA 1987a; Drill et al. 1981; Kimbrough 1987a). Monitoring data do not adequately characterize exposure levels for the reasons indicated in

Sect. 4.3.2.1 on liver effects in humans after inhalation exposure. Also, correlations between chloracne and duration of exposure or blood concentrations of Aroclors are poor or nonexistent. Drill et al. (1981) concluded that individuals with blood levels of ≥200 ppb of PCBs have an increased risk of chloracne and that chloracne may occur more frequently in workers exposed to PCBs that have been heated and to PCBs that have ≥54% chlorination. The conclusions of Drill et al. (1981), however, are based on Kanechlor as well as Aroclor toxicity data. As chloracne is reported frequently among workers who were exposed to Kanechlors, the higher chloracnogenic potential of Kanechlors and heated Aroclors may be related to higher levels of PCDFs and polychlorinated quaterphenyl contaminants (Drill et al. 1981).

In one study, 34 workers who were exposed to Aroclor 1242 at concentration between 0.32 and 2.22 mg/m^3 for 5 to 23 years in an electrical plant complained of burning of the eyes, face, and skin; five had eczematous rashes on the hands and legs (Ouw et al. 1976). Aroclor 1242 was reported to be free of impurities.

Inhalation, animal. Pertinent data were not located in the available literature.

Oral, human. Pertinent data were not located in the available literature.

Oral, animal. Cutaneous effects occurred in rhesus monkeys fed diets that contained Aroclors for subchronic durations (Allen and Norback 1973, Allen et al. 1974a, Allen 1975, Barsotti and Allen 1975, Barsotti et al. 1976, Thomas and Hinsdill 1978, Becker et al. 1979, Allen et al. 1979, McNulty et al. 1980). These include facial (particularly periorbital) edema, purulent discharge from the eyes, chloracne, and alopecia. The effects appear to be reversible and have been produced by diet exposures as low as 2.5 ppm Aroclor 1248 for 1 to 6 months (Barsotti and Allen 1975) and 3 ppm Aroclor 1242 for 6 months (Becker et al. 1979). NOAELs were not identified in the available studies.

In the Barsotti and Allen (1975) study, rhesus monkeys were fed diets containing 2.5 or 5.0 ppm Aroclor 1248 for 1 year. The animals exposed to 2.5 ppm (all females) developed periorbital edema, alopecia, erythema, and acneform lesions of the face and neck within 1 to 2 months. The males treated at 5.0 ppm had only moderate periorbital edema and erythema.

Thomas and Hinsdill (1978) fed 0, 2.5, and 5.0 ppm Aroclor 1248 to adult female rhesus monkeys. All eight monkeys in each Aroclor-treated group developed alopecia, chloracne, and facial edema after 6 months of treatment.

In the Becker et al. (1979) study, six young (7 to 8 months old) monkeys were fed diets containing 0, 3, 10, 30, or 100 ppm Aroclor 1242 (two were fed 10 ppm). Facial changes (palpebral swelling and erythema but no loss of hair) were evident by the end of the second month at ≥10 ppm and in the sixth month at 3 ppm; mortality was 4/6 by day 245, including the monkey fed 3 ppm.

Rats exposed to Aroclor 1254 in the diet developed alopecia, facial edema, and exophthalamos after 104 weeks of 50 ppm and 72 weeks of 50 ppm (NCI 1978); these effects did not occur after 104 weeks of 25 ppm.

In a single-dose study, thickening and erythema of the pinna of the ear occurred in mice exposed to 200 ppm of Aroclor 1254 in the diet for 23 weeks (Bell 1983).

All of the above studies did not report possible impurities.

Dermal, human. Pertinent data were not located in the available literature.

Dermal, animal. Daily application of 118 mg Aroclor 1260 (free of PCDF) in isopropanol vehicle to the shaved backs of four female New Zealand rabbits 5 days/week for 38 days produced thickening of the skin and acneform lesions resulting from hyperplasia and hyperkeratosis of the epidermal and follicular epithelium (Vos and Beems 1971). These results were verified in another similarly designed study (Vos and Notenboom-Ram 1972).

General discussion. Relatively small groups of animals were tested in most of the studies, but the cutaneous effects are well characterized. The cutaneous effects in occupationally exposed humans are generally consistent with the animal data, but effect levels cannot be ascertained and the contribution of direct skin exposure or contaminants cannot be evaluated with the information reported in the papers.

4.3.2.3 Immunological effects

Inhalation, human. Significant alterations in various globulin fractions have not been observed in Aroclor-exposed workers (Ouw et al. 1976; Smith et al. 1981a,b,c).

Inhalation, animal. Pertinent data were not located in the available literature.

4.3.2.4 Oral

Human. Pertinent data were not located in the available literature.

Animal. Female guinea pigs maintained on diets that contained 50 ppm of Aroclor 1260 for 6 weeks had significantly lowered tetanus autotoxin titers, circulating leukocytes and lymphocytes, and thymus atrophy (Vos and van Genderen 1973). Exposure to 10 ppm Aroclor 1260 in the diet for 8 weeks produced splenic atrophy in guinea pigs (Vos and de Roij 1972). NOAELs were not identified in these studies. The Aroclor 1260 used in these studies was reported to be free from PCDF impurities.

Thomas and Hinsdill (1978) exposed groups of 5 to 8 female rhesus monkeys to 0, 2.5, or 5.0 ppm Aroclor 1248 in the diet for 11 months. Significantly lower antibody response to sheep red blood cells occurred at 5.0 ppm. There was no treatment-related effect on antibody response to tetanus toxoid.

Barsotti et al. (1976) also found evidence of an immunological effect in rhesus monkeys fed 2.5 or 5.0 ppm Aroclor 1248 in the diet for 7 months prior to mating and during pregnancy. Monkeys developed shigellosis during and after treatment, indicating an increased susceptibility to infection.

Thomas and Hinsdill (1978) also fed Aroclor 1248 to mice at 100 or 1000 ppm in the diet for 3 to 5 weeks. The mice had enhanced sensitivity to *Salmonella typhimurium* and endotoxin, indicating lowered resistance to infection.

Dermal, human. Pertinent data were not located in the available literature.

Dermal, animal. Dermal application of 120 mg/day Aroclor 1260 (free of PCDF impurities) in isopropanol 5 days/week for 4 weeks produced moderate thymic atrophy in rabbits (Vos and Notenboom-Ram 1972). Similar application of 118 mg/day Aroclor 1260 for 38 days produced histological atrophy of the thymus cortex and a reduction in the number of germinal centers in the spleen and lymph nodes in rabbits (Vos and Beems 1971).

General discussion. The Thomas and Hinsdill (1978) study suggests that the threshold for immunosuppression in monkeys is in the diet concentration range of 2.5 to 5.0 ppm. Treatment of rodents with oral or dermal doses of Aroclors, non-Aroclor PCBs, and/or individual PCB congeners that have a different composition than those covered by this profile has also produced effects on the immune system. This is illustrated in the study by Biocca et al. (1981) in which a decrease in thymus weight was observed in mice exposed to 3,4,5-symmetrical hexachlorobiphenyl for 5 weeks in the diet at 10 ppm, compared with similar effects produced at levels of 300 ppm for 2,4,5- or 2,4,6-symmetrical hexachlorobiphenyl or at 167 ppm Aroclor 1242 in the diet of mice in a 6-week study (Loose et al. 1978a,b). These effects include immunosuppression as measured by increased mortality to *Salmonella typhosa* lendotoxin and *Plasmodium berghei* in mice given 167 ppm Aroclor 1016 or 1242 in the diet for 6 weeks (Loose et al. 1978a,b), and increased mortality caused by *S. typhimurium* endotoxin in mice that were given 100 or 1000 ppm Aroclor 1248 in the diet for 5 weeks (Thomas and Hinsdill 1978). PCBs also caused splenic, thymic, and lymph node atrophy in rats (Allen et al. 1975, Allen and Abrahamson 1973, Parkinson et al. 1983).

Although PCBs appear to be immunosuppressive in animals, the effect of PCBs on immune system function in humans has not been adequately evaluated. Based on animal splenic and lymphoid system histological alterations, Drill et al. (1981) speculated that significant immunosuppression in humans may occur only at high dosages secondary to malnutrition (i.e., via general toxic responses such as decreased food intake, decreased body weight, or decreased body weight gain).

Immunotoxicity of PCBs appears to be dependent upon expression of the aromatic hydrocarbon receptor and on the ability of PCBs to bind to the receptor (EPA 1987a). The receptor binding affinity of PCBs is dependent on the molecular conformation that is determined by the chlorine substitution pattern.

4.3.2.5 Thyroid

Inhalation. Pertinent data were not located in the available literature.

Oral, human. Pertinent data were not located in the available literature.

Oral, animal. Rats exposed to Aroclor 1254 for 4 to 12 weeks experienced thyroid alterations that included enlargement, reduced follicular size, follicular cell hyperplasia, and accumulation of colloid droplets and large, abnormally shaped lysosomes in the follicular cells (Collins et al. 1977; Collins and Capen 1980b,c; Kasza et al. 1978). The thyroid alterations resulted in reduced serum thyroxine levels and appear to be reversible after cessation of exposure. None of these studies reported the purity of the Aroclor 1254 sample used.

Collins and Capen (1980b) exposed groups of six male Osborne-Mendel rats to 0, 5, 50, or 500 ppm Aroclor 1254 in the diet for 4 weeks. Histological and ultrastructural effects consistent with those described above occurred at ≥5 ppm, and reduced serum thyroxin occurred at ≥50 ppm. A NOAEL for thyroid alterations cannot be discerned from the available studies.

Dermal. Pertinent data were not located in the available literature.

General discussion. Although effects of Aroclor exposure on the thyroid have been investigated in only a few studies, this gland is an unequivocal target of Aroclor in rats. The lowering of serum thyroxine by Aroclors appears to be the combined result of a direct effect on thyroid follicular cells with an interference in hormone secretion plus an enhanced peripheral metabolism of thyroxine (Collins et al. 1977).

Ultrastructural lesions in thyroid follicular cells and reductions in serum levels of thyroid hormones (thyroxine and triiodothyronine) occurred in neonatal and weanling rats whose dams were fed diets containing 50 or 500 ppm Aroclor 1254 throughout gestation and lactation (Collins and Capen 1980a). These authors also reported that other studies have found that decreased reproductive performance and interference in growth and development occurred in man and animals that were rendered hypothyroid and that PCBs enhance the peripheral metabolism and excretion of thyroxine-glucuronide in the bile. These findings and the thyroid effects in Aroclor-exposed adult rats summarized previously suggested to Collins and Capen (1980a) that some of the well-documented PCB-related disturbances in reproduction, growth, and development may be related to alterations in thyroid structure and function in the dam, fetus, or neonate.

4.3.2.6 Stomach

Effects on the stomach have been studied only in animals exposed orally. Oral administration of Aroclor 1248 (Allen and Norback 1973; Allen et al. 1974a,b; Allen 1975; Barsotti and Allen 1975) and Aroclor 1242 (Becker et al. 1979) to monkeys produced gastritis, which progressed to hypertrophy and hyperplasia of the gastric mucosa. Related

effects include mucous-filled cysts that penetrate the muscularis mucosa. These effects were initiated by exposures as low and/or short as a single gavage dose of 1.5 g/kg of Aroclor 1248 (Allen et al. 1974a), 25 ppm of Aroclor 1248 in the diet for up to 1 year (Barsotti and Allen 1975), and 3 ppm of Aroclor 1242 for 71 days (Becker et al. 1979).

The Aroclor-induced gastric lesions occurred only along the greater curvature of the stomach (not in the cardiac or pyloric regions, which are more usual regions for gastric effects), did not occur in other sections of the gastrointestinal tract, and have not been observed in species other than monkeys (Becker et al. 1979, Drill et al. 1981). These gastric effects may therefore be species specific. Aroclor 1254-induced metaplasia and adenocarcinoma in the glandular stomach of F344 rats have been reported (Morgan et al. 1981) (Section 4.3.6 on carcinogenicity in this section). These studies did not report the purity of the Aroclor sample used.

4.3.2.7 Porphyria

Inhalation, human. Exposure-related urinary porphyrins, porphyrin-related disease, or cases of porphyria cutaneous tarda have not been reported in clinical studies of Aroclor-exposed workers (Alvares and Kappas 1979; Fischbein et al. 1979; Smith et al. 1981a,b,c).

Inhalation, animal. Pertinent data were not located in the available literature.

Oral, human. Pertinent data were not located in the available literature.

Oral, animal. Groups of six male Sprague-Dawley rats were treated with 0, 5, or 25 ppm of Aroclor 1242 (purity not reported) in the diet for 2, 4, or 6 months (Bruckner et al. 1974). Urinary coproporphyrin levels were increased in rats treated at both concentrations.

Dermal, human. Pertinent data were not located in the available literature.

Dermal, animal. Fecal coproporphyrin was elevated in female New Zealand rabbits that received a 120-mg application of Aroclor 1260 to shaved backs 5 days/week for 4 weeks (Vos and Notenboom-Ram 1972). Fecal coproporphyrin and protoporphyrin were increased in rabbits similarly treated with 118 mg/day Aroclor 1260 5 days/week for 36 days (Vos and Beems 1971). The Aroclor 1260 used in these studies was free of PCDF.

General discussion. Goldstein et al. (1974) found that onset of porphyria was delayed in rats fed a higher concentration (100 ppm) of Aroclor 1254, occurring after 2 or 7 months of treatment, and that there was an increase in delta-aminolevulinic (ALA) synthetase activity. Other results of this study suggest that PCBs may affect uroporphyrin formation or utilization, rather than induction of ALA synthetase (the increase in ALA synthetase activity was probably secondary to the porphyria) (Drill et al. 1981). Induction of ALA synthetase (a rate-limiting enzyme in heme synthesis) is the mechanism of porphyrogenic action of many other chemicals (Drill et al. 1981, Hill 1985).

Although porphyria has not been reported in Aroclor-exposed humans, Drill et al. (1981) observed that occurrence of increased ALA synthetase activity in treated animals raises the possibility that PCBs can cause an attack of porphyria in patients suffering from acute, intermittent porphyria. Chronic hepatic porphyria and porphyria cutanea tarda are associated with exposure to other polyhalogenated compounds, including polybrominated biphenyls and 2,3,7,8-TCDD (Hill 1985).

4.3.2.8 Kidney

The only study that reported effects on the kidneys was Vos and Beems (1971). In this study, Aroclor 1260 in isopropanol vehicle was applied to the shaved backs of New Zealand rabbits for 5 days/week at a dose of 118 mg/day for 38 days. Hydropic degeneration of the convoluted tubules, destruction of tubular epithelial cells, tubular dilation, and proteinaceous casts were observed. No mention of kidney effects was made in the study by Vos and Notenboom-Ram (1972), in which Aroclor 1260 was applied to the shaved backs of rabbits at 120 mg/day, 5 days/week for 28 days.

4.3.3 Developmental Toxicity

4.3.3.1 Inhalation

Human. Fifty-one infants born to women employed at two capacitor-manufacturing facilities with a history of high exposure to Aroclors 1254, 1242, and/or 1016 had mean birth weights and mean gestational ages that were lower than infants born to women who had worked in low-exposure areas (Taylor et al. 1984). The differences were small (153 g and 6.6 days), and the birth weight difference appears to have resulted from the shortened gestation rather than from a retardation of intrauterine growth. High-exposure workers were exposed to Aroclor during the manufacturing process for at least 1 year prior to the birth of the infant.

Animal. Pertinent data were not located in the available literature.

4.3.3.2 Oral

Human. Birth weight, length, head circumference, gestational age, and neonatal behavior were evaluated in 313 newborn infants (Fein 1984, Fein et al. 1984, Jacobson et al. 1984a). Of these infants, 242 were born to mothers who had consumed moderate to large quantities of Lake Michigan fish sometime during their lives, and 71 were born to mothers who did not consume Lake Michigan fish. Mean (± standard deviation) fish consumption and duration of consumption were 6.7 ± 5.8 kg/year and 15.9 ± 9.1 kg/year, respectively; consumption during pregnancy was 4.1 ± 4.4 kg/year. Maternal serum PCB concentrations averaged 5.5 ± 3.7 ng/mL, which reportedly is comparable to those for other midwestern area samples, and umbilical cord serum PCB levels averaged 2.5 ± 1.9 ng/L. Both maternal consumption of fish and levels of PCBs in cord serum were positively correlated with lower birth weight, smaller head circumference, and shorter gestation (Fein et al. 1984). Infants of mothers who had consumed contaminated fish were, on the average, 190 g

lighter, had head circumferences 0.6 cm less, and were born 4.9 days earlier than infants of mothers who hconsumed contaminated fish. Similar values were datsrminad whan infants with cord sarum levels ≥3 ng/mL ware compared with infants whose cord levels ware <3 ng/mL (the analytical quantification limit) (160 g lighter, 0.6 cm less in head circumference, 8.8 days less in gestational age). Head circumference was significantly smaller in both analyses even after birth weight and gestational age wars statistically controlled. Contaminated fish consumption was also positively correlated with impaired autonomic maturity, increased numbers of abnormal reflexes, and decreased range of state (Jacobson et al. 1984b). Range of state is a neurological category that includes peak of excitement, rapidity of build-up, irritability, and lability of state.

Rogan et al. (1986) examined birth weight, head circumfersnce, and the results of behavioral tests in 930 children. At birth, samples of placenta, maternal and cord serum, and milk were collected and analyed for PCBs. There was no correlation between birth weight or head circumference with PCB levels. Levels of PCBs in milk fat at birth of 3.5 to >4 ppm, but not <3.49 ppm, were significantly correlated with less muscle tone, decreased activity, and abnormal reflexes. The levels of PCBs to which these infants were exposed were probably as high as those encountered in the general population.

Jacobson et al. (1985) studied the effect of intrauterine exposure or exposure through breast milk to PCBs on visual recognition memory and preference for novelty in 123 infants. Measures of exposure included reports by the mothers of contaminated fish consumption, and analysis of cord serum levels and breast milk levels of PCBs. Reports of fish consumption and cord serum levels were predictors of poor visual recognition memory, while breast milk levels were not. There was a dose-related decrease in fixation to novelty: cord serum levels of 0.2 to 1.1 ng/mL were associated with mean scores of 61%, 1.2 to 2.2 ng/mL with mean scores of 60%, 2.3 to 3.5 ng/mL with scores of 57%, and 3.6 to 7.9% with scores of 50%.

Animal. Rabbits were exposed to 0, 1.0, or 10.0 mg/kg/day and 12.5, 25.0, or 50 mg/kg/day Aroclor 1254 (purity not reported) by gavage on days 1 to 28 of pregnancy in separate experiments (Villeneuve et al. 1971). Abortions, stillbirths, and maternal deaths occurred at ≥12.5 mg/kg/day, but there were no treatment-related teratogenic effects at any dose level. It was noted that unpublished data from the same laboratory showed that administration of Aroclor 1221 at doses ≤25 mg/kg/day was not fetotoxic to rabbits (Villeneuve et al. 1971).

Doses of 0, 6.25, 12.5, 25, 50, or 100 mg/kg/day of Aroclor 1254 were administered by gavage on days 6 to 15 of gestatior to rats (Villeneuve et al. 1971). Average pup weights were reduced at 100 mg/kg/day, although total litter weight (average weight times number of fetuses) did not differ from controls. There were no skeletal or visceral abnormalities or effects on conception, resorptions, litter size or number, or average litter weight in any of the treated groups. In other rat studies with Aroclor 1254 (purity not reported), reduced average fetal weight per litter (Spencer 1982) and reduced pup survival

and body weight at weaning (Linder et al. 1974) resulted from 100 mg/kg/day gavage exposure on days 6 or 7 to 15 of gestation.

Collins and Capen (1980a) fed diets containing 0, 50, or 500 ppm Aroclor 1254 (purity not reported) to groups of 15 female Osborne-Mendel rats throughout pregnancy and lactation. There was a statistically significant ($P < 0.001$) reduced litter size in the 500-ppm groups compared with controls. Statistically significant decreases in pup body weight were observed at 50 and 500 ppm in 21-day-old pups, but not at 7 or 14 days or at parturition. Ultrastructural lesions in thyroid follicular cells and reduction in serum levels of thyroid hormone (thyroxine and triiodothyronine) occurred in the neonatal and weanling rats at 50 and 500 ppm. Although pups are not usually examined for effects on the thyroid in developmental studies, the observation of thyroid effects in the neonates can be considered a fetotoxic effect because the thyroid is a target organ of Aroclor 1254 toxicity. Assuming that a rat consumes a daily amount of food equal to 5% of its body weight (EPA 1986a), the 50- and 500-ppm levels are equivalent to doses of 2.5 and 25 mg/kg/day, respectively; therefore, 2.5 mg/kg/day is the LOAEL for fetotoxicity in rats.

Haake et al. (1987) reported that treatment of pregnant C57BL/6 mice with Aroclor 1254 by gavage at 244 mg/kg on day 9 of gestation did not result in any fetuses with cleft palate.

Groups of eight female monkeys were maintained on diets containing 0, 0.25, or 1.0 ppm of Aroclor 1016 (free of PCDF) in the diet for approximately 7 months prior to mating and during pregnancy (Barsotti and Van Miller 1984). Mean birth weight in the 1.0-ppm group was significantly ($P < 0.01$) less than controls, but head circumference and crown-to-rump length were unaffected. All females conceived, carried their infants to term, and delivered viable offspring. More pronounced fetotoxic effects (early abortions or resorption, stillbirths, and/or reduced birth weight), lengthened menstrual cycles, and lowered serum progesterone levels occurred in monkeys exposed to 2.5 or 5.0 ppm Aroclor 1248 (purity not reported) in similarly designed studies (Allen and Barsotti 1976; Allen et al. 1979, 1980).

4.3.3.3 Dermal

Pertinent data were not located in the available literature.

4.3.3.4 General discussion

Comprehensive teratological examinations have not been conducted; however, the above studies and others (EPA 1987a) indicate that Aroclors were not teratogenic in rats and nonhuman primates when tested via the oral route during the critical periods of organogenesis at doses that produce fetotoxicity and/or maternal toxicity. Although fetotoxicity of Aroclors is documented in several species of animals, the possibility that contaminants (e.g., PCDFs) may be responsible for the effects should be recognized.

Reports of reduced birth weight and gestational age in infants of mothers with occupational and environmental exposure to Aroclors (Taylor et al. 1984, Fein 1984, Fein et al. 1984) are inconclusive but consistent with the animal developmental effects data. Although serum

levels of PCBs were correlated with these effects, the effects may not be specific to PCB contamination because the fish were also contaminated with other pollutants. The birth weight decreases are of the same order of magnitude as that reported by the Surgeon General for smoking during pregnancy (Fein 1984). Infants born to mothers who were exposed to Kaneclor PCBs during the Yusho incident had signs of toxicity and delayed development (e.g., abnormal skin pigmentation, ocular discharge, small size), but no developmental abnormalities (EPA 1987a, Miller 1985). These effects did not persist. As discussed earlier in this profile, the Yusho incident was a unique event in which effects may not be related to PCBs.

Higher concentrations of PCBs in breast milk than in cord serum have led some investigators to assume that postnatal lactation exposure poses a greater threat to infants than intrauterine exposure. Jacobson et al. (1985) indicated that this assumption may be inappropriate because, relative to body weight, even low prenatal exposure can be substantial. Also, fetuses may be particularly sensitive to toxic insult because of factors such as lack of protective barriers (i.e., blood-brain) and metabolizing capacities that are found postnatally. That intrauterine exposure may be more harmful than postnatal exposure is also suggested by the results of the Jacobson et al. (1985) study, which indicated that behavioral effects were correlated more with prenatal exposure (cord serum PCBs) than with exposure via breast milk.

4.3.4 Reproductive Toxicity

Data for reproductive effects in animals were available only for oral exposure.

Groups of 12 female and 4 male mink were maintained on diets that provided 0, 1, 5, or 15 ppm Aroclor 1254 (purity not reported) for 4 months and were mated (Aulerich and Ringer 1977). Dose-related impaired reproduction (reduced number of females whelped and reduced kit/female ratio) occurred at ≥5 ppm, with total inhibition of reproduction at 15 ppm. These effects were also produced at 2 ppm Aroclor 1254 in a similarly designed single-dose level study; however, these effects did not appear to result from adverse effects on spermatogenesis (Aulerich and Ringer 1977). Complete reproductive failure occurred in mink exposed to ≥5 ppm Aroclor 1242, and Aroclor 1016 reduced but did not completely eliminate mink reproduction at 20 ppm (Bleavins et al. 1980). The rat appears less sensitive, with fetal mortality and maternal toxicity reported after daily consumption for 9 weeks of Aroclor 1254 at a level of 6.4 mg/kg/day (Baker et al. 1977). The purity of the Aroclors was not reported.

Rats were exposed to 0, 1, 5, 20, 100, or 500 ppm of Aroclor 1254 (purity not reported) in the diet in 1- and 2-generation reproduction studies (Linder et al. 1974). Reduced litter sizes occurred in the F_{1b} and F_2 generations at ≥20 ppm.

In longer-term studies (Allen et al. 1979b, 1980; Barsotti et al. 1976), monkeys were exposed to Aroclor 1248 in the diet at levels of 2.5 and 5.0 ppm for 18 months. Maternal toxicity that included lengthened menstrual cycles was observed. At the high-dose level, there was nearly complete inhibition of reproduction, while at the low-dose

MONS 027340

there were early abortions and fatal resorptions, although some live births did occur. Although this indicates that the monkey was very sensitive to the reproductive toxicity of Aroclor 1248, it should be noted that chemical analyses indicated that the PCBs were contaminated with approximately 1.7 ppm of PCDFs, which may have contributed to the observed toxicity.

Reproductive effects resulting from higher oral doses of Aroclor prior to and during gestation include prolonged estrous cycle and decreased sexual receptivity in rats (Brezner et al. 1984), reduced conception rate in mice (Welsch 1985), and reduced litter size in rats (Linder et al. 1974). Lactation exposure produced decreased reproductive capacity in male rats (Sager 1983) and premature vaginal opening and delayed first estrus in female rats (Brezner et al. 1984).

4.3.5 Genotoxicity

4.3.5.1 Human

No data were located in the available literature.

4.3.5.2 Nonhuman

Results of mutagenicity assays with PCBs in in vitro systems are summarized in Table 4.3. Results of studies using PCB mixtures other than Aroclors are included to provide additional information. PCBs gave generally negative results in *Salmonella typhimurium*, with and without metabolic activation. The only positive responses were obtained by Wyndham et al. (1976), who observed increases in reversion frequency in *Salmonella typhimurium* strain TA1538 exposed to 4-chlorobiphenyl and, to a lesser extent, Aroclor 1221 only in the presence of metabolic activation. Negative results were obtained with the more highly chlorinated Aroclor 1254 and 2,2',5,5'-tetrachlorobiphenyl. These data suggested that the less chlorinated PCBs may be metabolized to mutagenic compounds to a greater extent than the more chlorinated PCBs (EPA 1985a). Harbison (1986) discounted the positive results of the Wyndham et al. (1976) study because of the inability of one of the authors to reproduce those findings and because of negative results in all of the other bacterial test systems.

PCBs gave generally negative results in in vivo assays with rats and mice (Table 4.4). Weakly positive results (chromosomal aberrations) were obtained in ring dove (*Streptopchia risoria*) embryos from doves fed Aroclor 1254 at 10 ppm in the diet.

4.3.6 Carcinogenicity

4.3.6.1 Inhalation

Human. Bahn et al. (1976, 1977) reported an increased incidence of malignant melanomas in employees of a northeastern U.S. petrochemical plant where Aroclor 1254 was used for 9 years in the 1950s. Two of 31 heavily exposed workers developed malignant melanomas. This incidence was significantly above the expected rate. Quantitative exposure data were not reported.

MONS 027341

Table 4.3. Genotoxicity of PCBs in vitro

End point	Species (test system)	Result with activation/without activation	References
Gene mutation	*Salmonella typhimurium*	−/−	Schoeny et al. 1979, Schoeny 1982, Heddle and Bruce 1977, Wyndham et al. 1976
	Chinese hamster V79 cells	−/−	Hattula 1985
Chromosomal aberrations	Human lymphocytes	−	Hoopingarner et al. 1972

MONS 027342

Table 4.4. Genotoxicity of PCBs in vivo

End point	Species (test system)	Result	References
Chromosomal aberration	*Drosophila melanogaster*	–	Nilsson and Ramel 1974
	Ring dove (*Streptopchia risoria*)	+	Peakall et al. 1972
	Chicken	–	Blazak and Marcun 1975
	Mouse	–	Watanabe and Sugahara 1981
	Rat	–	Green et al. 1975a, Garthoff et al. 1977, Dikshith et al. 1975
Dominant lethal	Mouse	–	Green et al. 1975b, Keplinger et al. 1971, Calandra 1976

MONS 027343

Brown and Jones (1981) conducted a cohort mortality study of 2567 workers in two capacitor factories where PCBs were used. All-cause mortality and cancer mortality were lower than expected. Excess mortality was observed for rectal cancer and liver cancer, but neither was statistically significant. Monitoring data were not reported.

Gustavsson et al. (1986) performed a cohort study of 142 male Swedish capacitor-manufacturing workers who had been exposed to PCBs for an average of 6.5 years between 1965 and 1978. Airborne PCB levels measured in 1973 were 0.1 mg/m^3. It is not clear if this level represents an average for 1965-1978. Skin contamination had occurred in some of the workers. Seven cancers had occurred in these workers, which was in agreement with national statistics. One person had two rare tumors, a slow-growing mesenchymal tumor and a malignant lymphoma. The authors concluded that this study did not indicate any excess mortality or cancer incidence among PCB workers, but that such effects could not be ruled out because of the small cohort and relatively short follow-up period.

Davidorf and Knupp (1979) found no relationship between possible PCB exposure and increased annual occurrence of ocular melanoma in Ohio during 1967-1977.

Animal. No data were located in the available literature.

4.3.6.2 Oral

Human. Urabe et al. (1979) reported that by 1979, 31 Yusho patients had died, 11 from malignant neoplasms. These data were insufficient to determine if there was an increase in cancer among the exposed population.

Statistically significant excess risk of liver cancer has been reported in Yusho patients that were studied for a follow-up period of over 16 years (Amano et al. 1984, Kuratsune 1986). Because the excess of liver cancer was found in only one prefecture, the findings are considered tentative. Simultaneously with exposure to PCBs, the patients were also known to be exposed to PCDFs and polychlorinated quinones, which may have contributed to the excess risk of liver cancer. Further analysis of these studies is in progress. Although the findings are suggestive of a relation between oral exposure to PCBs and excess risk of liver cancer, the Carcinogen Assessment Group considers the present data inadequate (EPA 1987a).

Animal. Kimbrough et al. (1975) fed groups of 200 female weanling Sherman rats diets containing 0 or 100 ppm Aroclor 1260 (purity not reported). Aroclor treatment was discontinued 6 weeks before the rats were killed at 23 months of age. Mean final body weights and body weight gain were significantly ($P < 0.001$) reduced in the treated group, but food consumption in the two groups was comparable. Actual PCB intake in the treated rats was 11.6 mg/kg/day during the first week of exposure, 6.1 mg/kg/day at 3 months, and 4.3 mg/kg/day at 20 months. Almost all treated rats (170/184) exhibited a few to multiple tan nodules on the surface of the liver and more on sectioning. Only one control animal had gross abnormalities of the liver. Hepatocellular carcinomas were found in 1/173 (0.58%) controls and 26/184 (14%) treated rats. Neoplastic

nodules were found in the livers of 0/173 controls and 144/184 treated rats. The total incidence of neoplastic liver lesions was 1/173 (<1%) in controls and 170/184 (92%) in treated rats.

In a shorter preliminary study, Kimbrough et al. (1972) exposed groups of 10 male and female Sherman rats to 0, 100, 500, or 1000 ppm Aroclor 1254 (purity not reported) or 1260 in the diet for <1 year. No neoplastic nodules or hepatocellular carcinomas were found.

Norback and Weltman (1985) fed a group of Sprague-Dawley rats (70 per sex) a diet containing Aroclor 1260 (purity not reported) at a concentration of 100 ppm for 16 months, and 50 ppm for an additional 8 months, followed by a control diet for 5 months. A control group consisted of 63 rats per sex. In the treated rats examined after 18 months, 95% of the 47 females and 15% of the 46 males had hepatocellular neoplasms. This indicated a gender-related effect. Among treated females, 43/47 had trabecular carcinomas and/or adenocarcinomas, and another 2 females had neoplastic nodules only. Two of 46 treated males had trabecular carcinomas, and another 5 had neoplastic nodules. Incidences of hepatocellular neoplasms in control rats were 0/32 males and 1/49 females, the one female having a single neoplastic nodule. The progression of hepatocellular lesions was as follows: centrolobular cell hypertrophy at 1 month, foci of cell alteration at 3 months and areas at 6 months, neoplastic nodules at 12 months, trabecular carcinoma at 15 months, and adenocarcinoma at 24 months. The authors noted that while the tumors met morphologic criteria for malignancy, they were relatively unaggressive as they did not metastasize to distant organs or invade blood vessels. Mortality was not affected, probably because of the late appearance and slow growth of the tumors. Both treated and control rats developed cholangioma, cystic cholangioma, and adenofibrosis, but the incidence was greater in the treated group.

EPA (1987a) used the Norback and Weltman (1985) study as the basis for a carcinogenic risk assessment of PCBs using combined incidences of neoplastic nodules and hepatocellular carcinomas. Because this study demonstrated the progression of hepatocellular lesions through neoplastic nodules to carcinomas, it provides justification for using the combined incidences for quantitative risk assessment.

NCI (1978) exposed groups of 24 Fischer 344 rats per sex per dose to 0, 25, 50, or 100 ppm Aroclor 1254 in the diet for 104 to 105 weeks. Mean body weights of mid- and high-dose males and low-dose females were below those of controls from week 10 onward. There was a significant dose-related reduction in survival among treated males. There was a significant dose-related trend in combined incidences of lymphomas and leukemias in males, but incidences in each dose group were not significantly different from matched controls. NCI (1978) concluded that these tumors could not clearly be related to administration of Aroclor 1254. Hepatocellular adenomas and carcinomas were found in treated groups but not controls (males: mid-dose 1/24, high-dose 3/24; females: mid-dose 1/24, high-dose 2/24). Nonneoplastic hyperplastic nodules also occurred at a high incidence in treated animals but not controls. The tumor incidences were not significant, but the hyperplastic nodules appeared to be treatment related. Adenocarcinomas were found in the stomach, jejunum, or cecum of two treated males and two treated females.

and a carcinoma was found in one treated male. Although their incidence was not statistically significant, the low historical incidences of these lesions suggest that they might have been treatment related. NCI (1978) concluded that the high incidence of hepatocellular proliferative lesions in male and female rats was related to treatment, but that Aroclor 1254 was not carcinogenic in this bioassay. There was no attempt to identify or quantitate impurities.

Morgan et al. (1981) reexamined the NCI (1978) data with respect to gastric adenocarcinomas. Stomachs from rats used in that study were available for further sectioning and examination. Incidences of focal stomach lesions, mostly metaplasia, were 6, 10, 17, and 35% in rats receiving 0, 25, 50, and 100 ppm, respectively. Adenocarcinomas were found in six treated rats. When compared with incidences of stomach adenocarcinomas in historical controls (1/3548), the incidence 6/144 was significant at $P < 0.001$. The authors commented that adenocarcinoma and intestinal metaplasia appeared to be related and might have the same initiating mechanism. They concluded that Aroclor 1254 led to induction of intestinal metaplasia and probably to induction of adenocarcinoma in the glandular stomachs of F344 rats.

Ward (1985) also reexamined data from the NCI (1978) bioassay. He noted that hepatocellular adenomas, carcinomas, and eosinophilic and vacuolated hepatocellular foci usually occurred only in treated rats. It appeared that eosinophilic hepatocellular foci and tumors arose de novo rather than from naturally occurring basophilic foci. He suggested that Aroclor 1254 induced or initiated these unique lesions rather than promoted the growth of naturally occurring lesions. Ward (1985) also discussed the intestinal metaplasia and adenocarcinomas in treated rats. He noted that the metaplastic lesions were similar to those seen in monkeys, but differed in being focal and singular, while monkey lesions were diffuse. The appearance of the few metaplastic lesions in the stomachs of controls was different from those in treated rats, which resembled precancerous lesions induced by gastric carcinogens. Ward (1985) concluded that the effects of PCBs on the glandular stomach of rats should be studied further.

Kimura and Baba (1973) fed diets containing 38.5 to 616 ppm Kanechlor 400 to groups of 10 rats per sex for 159 to 538 days. Treated animals experienced significantly decreased body weight gain and other signs of toxicity. EPA (1985a) concluded that this study was too short and the doses too high to be useful for assessing carcinogenic potential of this PCB mixture.

Ito et al. (1974) exposed groups of 10 male Wister rats to 100 to 1000 ppm of Kanechlor 300, 400, or 500 in the diet for up to 1 year. Nodular hyperplasia, which was considered preneoplastic, was observed in a few of the treated rats. No significant tumorigenic effects were noted. EPA (1985a) judged this study to be inadequate because of its short duration and the small numbers of animals used.

Kimbrough and Linder (1974) fed groups of 50 male Balb/cJ mice diets containing 0 or 300 ppm Aroclor 1254 (purity not reported) for 11 months or for 6 months followed by a 5-month recovery period. Treated mice had enlarged livers and adenofibrosis, a possible premalignant lesion (EPA 1987a). Incidences of hepatomas were: 0/34 and 0/24 in two

control groups, 9/22 in the 11-month exposure group, and 1/24 in the 5-month exposure group. This study provided evidence of the potential hepatocarcinogenicity of PCBs in mice.

Ito et al. (1974) observed hepatocellular carcinomas (5/12 mice) and liver nodules (7/12) in dd mice fed 500 ppm of Kanechlors 500 for 32 weeks. This study provides supporting evidence for the hepatocarcinogenicity of PCB mixtures.

Because PCB mixtures are often contaminated with PCDFs, it is possible that the carcinogenic response of some PCB mixtures is due to or augmented by these contaminants. Schaeffer et al. (1984) fed male Wister rats diets containing 100 ppm Clophen A 30 (30% chlorines by weight) or Clophen A 60 (60% chlorines by weight) for 800 days. These PCB mixtures were reported to be free of furans. Hepatocellular carcinomas developed in 61% of the rats fed Clophen A 60. Only 3% of the Clophen A 30 treated rats developed hepatocellular carcinomas, while 89% had preneoplastic lesions. This study demonstrates that PCB mixtures free from contamination with furans elicit a carcinogenic response.

4.3.6.3 Dermal

Human. Human exposures to PCBs via both the dermal and inhalation routes are discussed under the inhalation data.

Animal. DiGiovanni et al. (1977) reported that Aroclor 1254 (purity not reported) showed weak initiator activity when applied to the skin of CD-1 mice. Berry et al. (1978) reported that Aroclor 1254 was not a skin tumor promoter in female CD-1 mice that had been initiated with DMBA, nor did it produce tumors when tested without DMBA initiation at a level of 1 mg administered twice weekly.

4.3.6.4 General discussion

The study by Kimbrough et al. (1975) demonstrated the hepatocarcinogenicity of Aroclor 1260 in female Sherman rats. A preliminary experiment using smaller groups of animals of the same sex and strain exposed for <1 year did not result in neoplastic nodules or hepatocellular carcinomas (Kimbrough et al. 1972). These results suggest that hepatocellular carcinomas caused by PCBs can be detected only in long-term experiments at doses low enough to prevent interfering toxicity. In addition, because the large long-term experiment only produced a 14% incidence of carcinomas, relatively large numbers of animals must be used to detect a significant increase in tumor incidence. Similarly, the NCI (1978) rat study with group sizes of 24 rats per sex was considered not sensitive enough to identify as significant an increase in tumor incidence of this magnitude (14%). The NCI (1978) study found hepatocellular carcinomas in 2/24 (8%) male rats fed 100 ppm Aroclor 1254. If incidences are expressed as the number of animals with tumor per number of animals at risk, as is more commonly done, the incidence is 2/20 or 10%. The 8 to 10% incidence is not detected as statistically significant with group sizes of 24 rats, nor would a 14% incidence, as was observed in the Kimbrough et al. (1975) study, be detected as statistically significant. EPA (1985a) concluded that the results of the NCI (1978) study did not by themselves demonstrate the carcinogenicity of Aroclor 1254, but they were

consistent with the positive results of the Kimbrough et al. (1975) study and supported them. EPA (1985a) stated that the carcinogenicity of Aroclor 1260 "appears to have been demonstrated" and the carcinogenicity of Aroclor 1254 was "suggested."

EPA (1985a) discussed the difficulties in using data from assays with commercial PCB mixtures for quantitative risk assessment. The composition of these mixtures is highly variable. Different lots of the same Aroclor, while having the same average chlorine content, can differ substantially in content of individual isomers. The metabolic and pharmacokinetic behavior of the pure isomers varies greatly with the degree and position of chlorine substituents. Analysis of an Aroclor 1254 lot indicated a predominance of pentachloro biphenyl isomers, which are relatively rapidly metabolized and excreted. An Aroclor 1260 lot was primarily hexa- and heptachloro isomers, which would be retained in adipose and skin storage depots for long periods. These storage depots might be considered effective removal of carcinogens from the target organs or, conversely, a carcinogen pool capable of mobilization and adding to target organ exposure. Different Aroclors administered at the same dosage could result in completely different tissue-specific exposure levels for the various pure isomers and metabolites. A potency estimate based only on administered dosage is therefore inappropriate. EPA (1985a) concluded that the potency of any commercial PCB mixture is probably higher than any estimate that would be derived by using dietary levels of exposure as a basis for calculation.

EPA (1985a) selected the Kimbrough et al. (1975) study as the basis for the carcinogenicity risk assessment for PCBs. More recently, the Norback and Weltman (1985) study was used for quantitative risk assessment in EPA (1987a), which supersedes the aforementioned assessment. The Norback and Weltman (1985) study was preferred because the strain of rats used (Sprague-Dawley) has a low incidence of spontaneous liver neoplasia, the duration of the study was for the life span of the rats, and there was a sequential progression of liver lesions to hepatocellular carcinomas.

The available epidemiological data do not indicate a consistent tumorigenic affect among people exposed to PCBs.

4.4 INTERACTIONS WITH OTHER CHEMICALS

Many of the interactive affects of PCBs with other chemicals are related to the capacity of PCBs for enzyme induction. Therefore, the effects of PCBs on toxicity of other compounds depend on the role of oxidative metabolism in the toxicity of those compounds. Reported effects of PCB pretreatment include increased metabolism and excretion of pentobarbital and decreased pentobarbital sleeping times (Chu et al. 1977, Villeneuve et al. 1972), increased mutagenicity of B(a)P (Hutton et al. 1979), and increased hepatotoxicity of halothane and vinylidene fluoride (Sipes et al. 1978, Conolly et al. 1979).

Increased dietary ascorbic acid may protect against some of the toxic effects of PCBs, such as altered enzyme activity and liver histopathology, perhaps by inhibiting lipid peroxidation (Chakraborty et al. 1978, Kato et al. 1981). The exact mechanism is not known.

MONS 027348

PCBs have had mixed effects on tumor development. Aroclor 1254 pretreatment protected mice from lung tumors but increased the number of mice with liver tumors 18 months after administration of *N*-nitrosodimethylamine (Anderson et al. 1983). Makiura et al. (1974) reported that Kanechlor 500 inhibited hepatocarcinogenicity of 3'-methyl-4-dimethylaminoazobenzene, *N*-2-fluorenylacetamide, and *N*-nitrosodiethylamine when administered orally to rats. Nagasaki et al. (1975) found that Kanechlor 400 and 500 enhanced the hepatocarcinogenicity of α-BHC in mice. PCBs promoted the development of enzyme-altered foci or hyperplastic nodules following treatment with nitrosamines (Oesterle and Deml 1983, Pereira et al. 1982) or *N*-2-fluorenylacetamide (Tatematsu et al. 1979).

Birnbaum et al. (1985) found that 2,3,3',4,4',5-hexachlorobiphenyl, but not 2,2',4,4',5,5'-hexachlorobiphenyl, when coadministered with 2,3,7,8-TCDD to mice during gestation resulted in a dose-related enhancement of the TCDD-induced hydronephrosis in mouse fetuses, but 2,3,3',4,4',5-hexachlorobiphenyl alone caused hydronephrosis in the mouse fetuses. 2,2',4,4',5,5'-Hexachlorobiphenyl did not induce hydronephrosis.

Haake et al. (1987) found that Aroclor 1254 antagonized the teratogenicity of 2,3,7,8-TCDD in mice. In this study, treatment of pregnant mice by gavage with Aroclor 1254 at 244 mg/kg on day 9 of gestation followed by 2,3,7,8-TCDD at 20 μg/kg on day 10 resulted in an 8.2% incidence of cleft palate. Treatment with 2,3,7,8-TCDD alone resulted in a 62% incidence of cleft palate. Aroclor 1254 alone was not teratogenic.

Bannister et al. (1987) found that Aroclor 1254 partially antagonized the 2,3,7,8-TCDD-induced microsomal enzyme induction and immunotoxicity in mice.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

PCBs are no longer produced or used in the United States; however, many of the transformers and capacitors which were produced with PCBs, and contain PCBs, are still in service. Therefore, these products constitute a potential source of exposure to the environment and to humans. Disposal of PCB materials is controlled by federal regulations.

5.2 PRODUCTION

PCBs have been commercially produced in the United States since 1929. Annual U.S. production of PCBs peaked in 1970 when 85 million pounds were produced. It was estimated that approximately 1000 million pounds of PCBs had been sold in North America since 1970. Manufacture of PCBs (Aroclors) in the United States was terminated in October 1977 because these products accumulated and persisted in the environment and because of their toxic effects. Monsanto, the sole U.S. manufacturer at that time, had been producing Aroclors 1016, 1221, 1242, and 1254. In 1974, Monsanto produced just over 40 million pounds of the Aroclor mixtures. Production had been approximately 40 million pounds annually since 1971. Monsanto produced PCB Aroclor products at a facility in Sauget, Illinois, but production was stopped in October 1977. Of the total PCBs sold in the United States since 1970, over 98% were Aroclor 1260, 1254, 1248, 1242, 1232, 1221, and 1016 and less than 2% were Aroclor 1268 and Aroclor 1262. Therefore, 98% of PCBs sold in the United States since 1970 have been covered in this document (IARC 1978, Hatton 1979, Durfee 1976, EPA 1976).

The Aroclors were prepared industrially by the chlorination of biphenyl with anhydrous chlorine in the presence of a catalyst such as iron filings or ferric chloride. The degree of chlorination, which determined which Aroclor was produced, was controlled by the anhydrous chlorine contact time in the reactor (EPA 1976).

5.3 IMPORT

Imports of PCBs through principal U.S. custom districts in recent years have been reported as follows (USITC, 1978, 1979, 1980, 1982):

Year	Import volume (lb)
1981	11,000
1979	357,147
1978	483,074
1977	280,867

MONS 027350

No date were located to indicate that PCBs have been imported after 1981.

Section 6(e)(3)(A) of TSCA (Pub. L. 94-469, 90 stat. 2003, 15U.S.C.2601 et seq) prohibits all manufacture and importation of PCBs as of January 1, 1979. As of January 2, 1979, EPA announced that companies that had filed petitions for exemptions from the PCB manufacturing/importation ban could continue the manufacturing or importation activity until EPA has acted on the application petition. (EPA 1979).

5.4 USES

A thorough review of PCB use in the United States can be found in EPA (1976). By 1974, all U.S. use of PCBs was in closed systems for the production of capacitors and transformers. As of 1976, 70% of Monsanto's domestic sales of Aroclors was used in capacitor production and 30% in transformer production. Aroclors are no longer used in the production of capacitors and transformers; however, many of the devices manufactured with Aroclors are still in service today. The life expectancy of transformers containing PCBs is >30 years, and the life expectancy of capacitors can range from 10 to >20 years, depending upon electrical application. PCBs were used in capacitors and transformers because of their excellent dielectric properties and fire resistance. Production of a large capacitor involved filling the capacitor with the Aroclor oil (typically over 2 to 3 lb of PCB) through a small hole and then sealing. Transformers were similarly filled, but may contain many times the amount of PCBs, depending on size. As of 1976, only 5% of the transformers produced in the United States were filled with PCBs, but 95% of the capacitors used PCBs (Durfee 1976). As of 1981, an estimated 131,200 PCB transformers were still in service in the United States, representing approximately 1% of all operational transformers (Orris et al. 1986).

5.5 DISPOSAL

On April 18, 1978, regulations became effective in the United States concerning the storage and disposal of PCBs. These regulations specified incineration as the only acceptable method of PCB disposal unless, by reason of the inability to dispose of the waste or contaminated material in this manner, clearance is obtained from the EPA to dispose of the materials in another way. In March 1983, the EPA issued a procedural amendment to the PCB rule to enable new disposal technologies to receive approval on a nationwide basis. At present, EPA's PCB disposal rules typically require that various types of PCBs and PCB materials be disposed of in chemical-waste landfills or destroyed in high-temperature incinerators or high-efficiency boilers. The disposal rules are published in the July 1984 Code of Federal Regulations, 40CFR, Part 761 (Kokoszka and Flood 1985, Hatton 1979).

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

At present, the major source of PCB exposure in the general environment appears to be environmental cycling of PCBs previously introduced into the environment. This cycling process involves volatilization from ground surfaces into the atmosphere with subsequent removal from the atmosphere via wet/dry deposition and then revolatilization. The environmental persistence of PCBs generally increases with an increase in the degree of chlorination of the congener. The Aroclors with a high degree of chlorination (1248, 1254, and 1260) are resistant to biodegradation and appear to be degraded very slowly in the environment. The chemical composition of the original commercial Aroclor mixtures which were released to the environment has changed over time since the individual congeners degrade and partition at different rates. Reviews of the environmental fate processes of PCBs are available (EPA 1987a, Leifer et al. 1983, Callahan et al. 1979).

6.2 RELEASES TO THE ENVIRONMENT

Since the Aroclors are no longer produced or used in the production of new products in the United States, industrial effluent discharges from production sources no longer occur. Current sources of PCB release to the environment include releases from landfills containing transformers, capacitors, and other PCB wastes, waste incineration of PCB materials, spills, and improper (or illegal) disposal to open areas (Weant and McCormick 1984, Murphy et al. 1985). In addition, explosions or overheating of transformers containing PCBs may release significant amounts of these materials into the local environment.

PCB emissions from landfills and incinerator stacks have been monitored (Murphy et al. 1985). This monitoring has indicated that the amount of PCBs released from these sources may not be significant when compared to estimated quantities of PCBs in the atmosphere.

Atmospheric fallout and washout have been identified as nonpoint sources of PCB exposure to the environment (Kleinert 1976, Weant and McCormick 1984, Swackhamer and Armstrong 1986, Larsson 1985). Although additional research is required for a definitive answer, evidence suggests that the current major source of PCB release to the environment is an environmental cycling process (Swackhamer and Armstrong 1986, Larsson 1985, Murphy et al. 1985). This cycling process involves volatilization of PCBs from bodies of water or from soil surfaces into the atmosphere. Once in the atmosphere, the PCBs are returned to earth via washout/fallout where the cycle is subsequently repeated with revolatilization. Since the volatilization and degradation rates of PCBs vary among the congeners present, this cycling process causes an

MONS 027352

alteration of the PCB ratio in water and air relative to the original source.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

In water, adsorption to sediments or other organic matter is a major fate process for the PCBs (EPA 1987a, Callahan et al. 1979). Experimental and monitoring data have shown that PCB concentrations are higher in sediment and suspended matter than in the associated water column. Based on their water solubilities and octanol-water partition coefficients, the lower chlorinated components of the Aroclors will sorb less strongly than the higher chlorinated isomers. Although adsorption can immobilize PCBs for relatively long periods of time in the aquatic environment, resolution into the water column has been shown to occur on an environmental level (Swackhamer and Armstrong 1986, Baker et al. 1985). The substantial quantities of PCBs contained in aquatic sediments can therefore act as an environmental sink for environmental redistribution of PCBs.

Volatilization is also an important environmental fate process for the PCBs that exist in natural water in the dissolved state. The values of the estimated Henry's law constants for the Aroclors (although they occur as a mixture in natural water) (see Table 3.2) are indicative of significant volatilization from environmental waters (Lyman et al. 1982). A study conducted on Lake Michigan has indicated that volatilization may be the major removal mechanism of PCBs from lakes (Swackhamer and Armstrong 1986). Strong PCB adsorption to sediment, however, significantly decreases the rate of volatilization, with the higher chlorinated Aroclors having longer volatilization half-lives than the lower chlorinated Aroclors (EPA 1985a). However, eventual resolution of PCBs from sediment into the water column can then result in volatilization.

The low water solubility, high octanol-water partition coefficients of the PCBs and demonstrated strong adsorption of PCBs to soils and sediment (EPA 1987a, Callahan et al. 1979, Sklarew and Girvin 1987) indicate that significant leaching should not occur in soil under most conditions. The tendency of the lower chlorinated PCBs to leach will be greater than the highly chlorinated PCBs. In the presence of organic solvents, PCBs can leach significantly in soil (Griffin and Chou 1981).

Organics having vapor pressures $>10^{-4}$ mm Hg should exist almost entirely in the vapor phase in the atmosphere, while organics having vapor pressures $<10^{-8}$ mm Hg should exist almost entirely in the particulate phase (Eisenreich et al. 1981). The vapor pressures of the Aroclors (see Table 3.2) indicate that they should therefore exist primarily in the vapor phase in the atmosphere. Monitoring data have shown that between 87 and 100% of the PCBs in air are operationally in the vapor phase (Eisenreich et al. 1981). The tendency of PCBs to adsorb to particulates will increase as the degree of chlorination increases.

PCBs in the atmosphere are physically removed by wet and dry deposition (Eisenreich et al. 1981). Dry deposition occurs only for the PCBs associated in the particulate phase. The PCB concentration of rain

anywhere in the world may typically range between 1 and 250 ng/L (Eisenreich et al. 1981), which is an indication of the importance of wet deposition.

6.3.2 Transformation and Degradation

The ability of PCBs to be degraded or transformed in the environment is dependent upon the degree of chlorination of the biphenyl molecule (EPA 1987a, Leifer et al. 1983, Callahan et al. 1979). In general, the persistence of PCB congeners increases as the degree of chlorination increases.

In the atmosphere, the vapor phase reaction of PCBs with hydroxyl radicals (which are photochemically formed by sunlight) may be the dominant transformation process. The estimated half-lives for this reaction in a typical atmosphere with various PCB isomers are as follows (EPA 1987c): monochlorobiphenyl, 12.9 days; dichlorobiphenyl, 27.8 days; trichlorobiphenyl, 1.43 months; tetrachlorobiphenyl, 3.1 months; pentachlorobiphenyl, 4.75 months; hexachlorobiphenyl, 10.3 months; and heptachlorobiphenyl, 1.31 years.

In the aquatic environment, transformation processes such as hydrolysis and oxidation do not significantly degrade PCBs (Mabey et al. 1981; Callahan et al. 1979). Photolysis appears to be the only viable chemical degradation process in water; however, sufficient experimental data are not available to determine its relative rate or importance in the environment (Leifer et al. 1983).

Reviews of the biodegradability of PCBs are available (EPA 1987a, Leifer et al. 1983). In general, the results show that mono-, di-, and trichlorinated biphenyls (Aroclors 1221 and 1232) biodegrade relatively rapidly, tetrachlorinated biphenyls (Aroclors 1016 and 1242) biodegrade slowly, and higher chlorinated biphenyls (Aroclors 1248, 1254, and 1260) are resistant to biodegradation. In addition to the degree of chlorination, chlorine positions on the biphenyl ring appear to be important in determining the biodegradation rate. For example, PCBs containing all of the chlorines on one ring are degraded faster than PCBs containing the chlorines distributed between both rings, and PCBs containing chlorines in the ortho positions are more resistant (Leifer et al. 1983). A study of subsurface aquatic sediments has shown that PCBs containing chlorines in the para positions are preferentially biodegraded as compared to other ring positions (Brown et al. 1987). This study of subsurface sediments, primarily from spill sites, has also shown that the higher chlorinated congeners are biotransformed by a reductive dechlorination to lower chlorinated PCBs which are biodegradable by aerobic processes. This is important since PCBs in soil systems or in aquatic sediments have not been shown to degrade by processes other than biodegradation. Therefore, biodegradation is probably the ultimate degradation process in soils and in sediments.

A summary of experimentally determined bioconcentration factors of various Aroclors (1016, 1248, 1254, and 1260) in aquatic species (fish, shrimp, oyster) has found Aroclor bioconcentration factors ranging from 26,000 to 660,000 (Leifer et al. 1983).

7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

PCBs partition significantly from water to aquatic organisms such as fish and can result in extremely high bioconcentration factors. Consumption of contaminated fish then results in human exposure to PCBs. Consumption of fish has been identified as a primary route of human exposure to PCBs. The general population is also exposed, on a continuel basis, to PCB levels in the breathable air. A review of environmental PCB monitoring data is available (EPA 1987a).

7.2 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

7.2.1 Air

Eisenreich et al. (1981) reported the following typical atmospheric concentrations of PCBs:

Location	Concentration range (ng/m^3)	Mean
Urban	0.5 to 30	5-10
Rural	0.1 to 2	0.8
Great Lakes	0.4 to 3	1
Marine	0.05 to 2	0.5
Remote	0.02 to 0.5	0.1

These values were derived from monitoring data reported in the literature.

Ambient atmospheric PCB concentrations of 7.1 and 4.4 ng/m^3 were detected in Boston, Massachusetts, and Columbia, South Carolina, respectively, during the summer of 1978 (Bidleman 1981). These concentrations are a composite for Aroclors 1016, 1242, and 1254. Anelysis of ambient air in Antarctica between 1981 and 1982 found PCB levels of 0.02 to 0.18 ng/m^3 (Tanabe et al. 1983).

The average PCB concentration (Aroclors 1242 and 1260) emitted from gas vents at a hazardous waste landfill in North Carolina was found to be 0.126 mg/m^3 (Lewis et al. 1985). PCB concentrations of 0.01 to 1.5 ppm were detected in the fly ash from five municipal incinerators operating under different technological and working conditions (Morselli et al. 1985). Stack effluents from several midwest municipal refuse and sewage incinerators contained PCB levels of 300 to 3000 ng/m^3 (Murphy et al. 1985). The total PCB concentration measured in the flue gas effluent from a municpal waste incinerator in Ohio was 260 ng/m^3 (Tiernan et al. 1983). PCBs were detected in effluents from combustion of coal and refuse at Ames, Iowa, at levels of 2 to 10 ng/m^3 (EPA 1987a).

MONS 027355

The average adult male inhales approximately 20 m^3 of air per day. Assuming the breathable outdoor air at a typical urban location contains an average PCB concentration of 5 ng/m^3, the average daily intake via inhalation would be 100 ng. This estimate pertains to background levels of PCBs in outdoor air. As reported in Sect. 7.4 (populations at high risk), PCB levels in certain indoor air may be an order of magnitude higher than in outdoor air.

7.2.2 Water

The concentration of PCBs in the oceans is an indication of the environmental background level in water. Concentrations reported for various seawaters include 0.04 to 0.59 ng/L in the north Pacific, 0.035 to 0.069 ng/L in the Antarctic, 0.3 to 3 ng/L in the southern North Sea, and 0.02 to 0.20 ng/L in the North Atlantic (Tanabe et al. 1983, 1984; Boon and Duinker 1986, Giam et al. 1978).

Mean PCB concentrations of 0.63 to 3.3 ng/L were detected in the waters of western Lake Superior during 1978 to 1983 monitoring (Baker et al. 1985). Mean levels of 3.0 to 9.0 ng/L (1974 to 1976) and 0.49 to 17.15 ng/L (1979 to 1981) were found in the water columns of Lake Michigan and Lake Huron, respectively (Rodgers and Swain 1983). Analysis of water from eight sites in Galveston Bay resulted in an average PCB level of 3.1 ng/L between 1978 and 1979 (Murray et al. 1981). Thirty-two of 163 wells monitored in industrialized areas of New Jersey were found to contain PCB levels ranging from 60 to 1270 ng/L (EPA 1987a). Mean PCB levels of 25 to 38 ng/L were detected in waters collected from 11 agricultural watersheds in Ontario during 1975 to 1977 (Frank et al. 1982). A discussion of a number of PCB monitoring studies conducted on the Hudson River can be found in EPA (1987).

Although PCBs are widespread in the aquatic environment, their low solubility generally prevents them from reaching high concentrations in drinking water supplies (EPA 1980a). The National Organic Monitoring Survey (NOMS) was conducted by the EPA to determine the frequency of occurrence of specific organic chemicals (including PCBs) in finished water supplies of 113 cities nationwide (EPA 1987a). Data from the three phases (referred to as NOMS I, II, and III) of the study were collected between March 1975 and January 1977. PCBs were not found in groundwater supplies sampled in NOMS I (minimum quantifiable limit of 0.12 ppb). Only a single finished groundwater sample in each of NOMS I and II contained detectable levels of PCBs; the concentration of each was reported to be 0.1 ppb (detection limits of 0.1 to 0.2 ppb). PCBs were detected in two finished surface water supplies in each of NOMS I and II and in one surface water in NOMS III; the concentrations of the five positive samples ranged from 0.1 to 1.4 ppb. A total mean PCB level of 0.12 to 0.8 ppb was found in tap water from the Waterford Water Co. (Hudson River source) in 1976 and 1977 (EPA 1987a, Kim and Stone, n.d.)

7.2.3 Soil

An analysis of 99 soil samples from rural and urban sites throughout Great Britain was conducted to determine background levels of PCBs in British soils (Creaser and Fernandes 1986). PCBs were identified in all samples within the range of 2.3 to 444 ppb ($\mu g/kg$). The mean and

median values found for all samples were 22.8 and 7.2 ppb, respectively. PCB levels ranging from 4.5 to 47.7 μg/kg have been detected in soil samples collected in the vicinity of incineration facilities in South Wales and Scotland during 1984 to 1985 (Eduljee et al. 1985, 1986). An analysis of Japanese soils detected PCB levels as high as 100 μg/kg; however, 40% of the samples had levels <10 μg/kg (Creaser and Fernandes 1986).

PCB concentrations ranging from <1 to 33 ppb have been detected in the soils of the Everglades National Forest in Florida (Requejo et al. 1979), which is consistent with the monitoring data from Great Britain. Carey et al. (1979a) analyzed soils from 37 states in 1972 as part of the National Soils Monitoring Program and found PCB in only 2 of 1483 soil samples; however, the analytical technique used had a minimum detectable limit of only 0.05 to 0.1 ppm, which was not low enough to detect the mean and median levels reported in Great Britain. Carey et al. (1979b) used the same analytical technique to analyze soils from five U.S. urban areas in 1971; positive detections were reported for three areas with PCB levels ranging from 0.02 to 11.94 ppm.

PCB levels of 0.098 to 0.54 mg/kg have been detected in the sediments from four remote high-altitude lakes in the Rocky Mountain National Park (Heit et al. 1984), which indicates levels of PCBs that can accumulate in sediments from natural deposition. Sediment core samples from the Milwaukee harbor, which has received industrial effluents of PCBs, have been found to contain levels of 1.03 to 13.4 mg/kg (Christensen and Lo 1986). Analysis of sediments from 19 selected streams in the Potomac River Basin found maximum PCB levels of 1.2 mg/kg (Feltz 1980). Upper sediment layers from the Hudson River and New York Harbor in 1977 contained Aroclor 1254 levels of 0.56 to 1.95 ppm and Aroclor 1242 levels of 3.95 to 33.3 ppm (Bopp et al. 1982). Analysis of surficial sediments from the Great Lakes and various associated waters found Aroclor 1254 levels of 2.5 to 251.7 ng/g, with the higher levels detected in Lake Erie (Thomas and Frank 1981). An average Aroclor 1260 concentration of 120 ng/g has been detected in sediment samples from eight sites along the coast of Maine (Ray et al. 1983).

7.2.4 Other

7.2.4.1 Foodstuffs

Table 7.1 lists the amounts of PCBs detected in raw domestic agricultural commodities during fiscal years 1970 to 1976. These commodities were analyzed as part of federal monitoring programs conducted by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture. It appears from Table 7.1 that fish are the primary foodstuff containing environmental background levels of PCBs; additional fish monitoring data are cited below. The contamination of fish is a consequence of the contamination of the aquatic environment and resulting bioconcentration (EPA 1980a).

Since the early 1960s, the FDA has conducted the Total Diet Studies, which have also been known as the Market Basket surveys. These studies, conducted on an annual basis, analyze ready-to-eat foods collected in markets from a number of cities nationwide to determine the

MONS 027357

Table 7.1. Aroclor residues in raw domestic agricultural commodities for fiscal years 1970–1976

Commodity	Number of samples analyzed	Percent with positive detections	Average concentration (ppm)
Fish	2,901	46.0	0.892
Shellfish	291	18.2	0.056
Eggs	2,303	9.6	0.072
Red meat[a]	15,200	0.4	0.008
Poultry	11,340	0.6	0.006
Fluid milk	4,638	4.1	0.067
Cheese	784	0.9	0.011

[a]Fiscal years 1973–1976.
Source: Duggan et al. 1983.

MONS 027358

intake of selected contaminants in the American diet. Table 7.2 presents the recent results of the Total Diet Studies with respect to PCBs. Since the mid-1970s, individual diets for adult males (19 years old), infants, and toddlers have been analyzed. Assuming that the average adult male weighs 70 kg and that the estimated dietary intake of PCBs is approximately 0.008 μg/kg/day (average of the three most recent figures reported in Table 7.2), the average daily intake via diet would be 0.56 μg (560 ng). This estimate indicates that consumption of food may be a major source of PCB exposure in humans; however, the source of the PCBs in food may be significant. In the recent years of the Total Diet Study, the primary source of PCBs in the diet has been in the food category meat-fish-poultry (Gartrell et al. 1986a, 1985a,b). FDA chemists have found that the source of the PCBs in the meat-fish-poultry composite is almost always due to the fish component (Jelinek and Corneliussen 1976). This suggests that persons consuming less than the average amounts of fish will be exposed to lower quantities of PCBs.

7.2.4.2 Fish and precipitation

The U.S. Fish and Wildlife Service has analyzed whole fish samples collected nationwide for PCB residues as part of the National Pesticide Monitoring Program (Schmitt et al. 1985). Between 1980 and 1981, 315 fish were collected from 107 stations nationwide. PCB residues were detected in 94% of all fish, with the geometric mean concentration of all Aroclors (wet weight) found to be 0.53 μg/g. This concentration is lower than previous monitoring in 1976 to 1977 and 1978 to 1979, which found concentrations of 0.88 and 0.85 μg/g, respectively. It should be noted that these fish analyses pertain to whole fish samples, which are composites of both the edible and nonedible portions of the fish. Therefore, the concentrations reported may not necessarily reflect the actual human exposure which will occur from oral consumption. Composite fish samples taken from major tributaries and embayments of Lake Superior and Lake Huron in 1983 contained PCB levels of 600 to 72,000 ng/g on a lipid basis (Jaffe et al. 1985). Analysis of 62 samples of commercial fish (primarily from Lake Ontario) collected in 1980 found levels of 0.11 to 4.90 ppm (Ryan et al. 1984).

Based on available monitoring data from the literature, the following PCB ranges (in ng/L) in rainwater appear to be typical at the various locations (Eisenreich et al. 1981): urban (10 to 250), rural (1 to 50), Great Lakes (10 to 150), marine (0.5 to 10), and remote (1 to 30). PCB levels of 0.160 to 1.0 ng/L have been detected in snow from the Antarctic (Tanabe et al. 1983). A review of PCB monitoring of precipitation is available (Mazurek and Simoneitt 1985).

7.3 OCCUPATIONAL EXPOSURES

It was estimated that approximately 12,000 U.S. workers were potentially exposed to PCBs annually from 1970 to 1976 (NIOSH 1977a). At present, however, PCBs are no longer industrially manufactured or used in the United States. Therefore, occupational exposure to those workers involved in producing PCBs or manufacturing products with PCBs should no longer occur. The potential for occupational exposure still exists, however, since PCB-containing transformers and capacitors remain in use.

MDNS 027359

Table 7.2. Estimated dietary intake of PCBs for adults, infants, and toddlers (μg/kg/day)

Fiscal year	Adult	Infant	Toddler
1981–1982	0.003	ND[a]	ND
1980	0.008	ND	ND
1979	0.014	ND	ND
1978	0.027	0.011	0.099
1977	0.016	0.025	0.030
1976	T[b]	T	ND

[a]ND = not detected.
[b]T = trace.
Source: Gartrell et al. 1985a,b,c and 1986a,b.

MONS 027360

Exposure may occur during repair or accidents of electrical equipment containing PCBs (Wolff 1985). Occupational exposure may also occur during waste site clean-up of PCB-containing waste sites.

7.4 POPULATIONS AT HIGH RISK

Several groups are at high risk from PCBs because of unusually high exposures. Persons occupationally exposed to PCBs are at high risk. Nursing infants may be exposed to high PCB concentrations in the breast milk of lactating women (EPA 1985a), especially if the women consume large amounts of contaminated fish.

Other subpopulations are at high risk from PCBs because they are more sensitive to toxic effects of exposure. Embryos, fetuses, and neonates are potentially susceptible because of physiological differences from adults. They generally lack the hepatic microsomal enzyme systems that facilitate detoxification and excretion of PCBs (Calabrese and Sorenson 1977, Gillette 1967, Nyhan 1961). Breast-fed infants have additional risk caused by a steroid excreted in human breast milk, but not cow's milk, that inhibits glucuronyl transferase activity and thus glucuronidation and excretion of PCBs (Calabrese and Sorenson 1977, Gartner and Arias 1966). Children exposed to the antibiotic novobiocin may also be at greater risk because novobiocin noncompetatively inhibits glucuronyl transferase activity in vitro (Lokietz et al. 1963, Calabrese and Sorenson 1977).

Other subpopulations that are potentially more sensitive to PCBs include those with incompletely developed glucuronide conjugation mechanisms, such as those with Gilbert's syndrome or Crigler and Najjar syndrome (Lester and Schmid 1964, Calabrese and Sorenson 1977). Persons with hepatic infections may have decreased glucuronide synthesis, making them more sensitive because of their decreased capacity to detoxify and excrete PCBs (Calabrese and Sorenson 1977).

The indoor air in a number of public buildings (schools, offices) was monitored in Minnesota during 1984 for Aroclors 1242, 1254, and 1260 (Oatman and Roy 1986). The total mean Aroclor concentration in the indoor air of buildings using PCB transformers was found to be nearly twice as high as buildings not using PCB transformers (457 vs 229 ng/m^3). It is also noteworthy that the levels found in all the indoor airs were significantly higher than in typical ambient outdoor air.

The indoor air in a number of laboratories, offices, and homes was monitored for various Aroclors. It was found that "normal" indoor air concentrations of PCBs can be 1 order of magnitude higher than those in the surrounding outdoor atmosphere (MacLeod 1981). It was suggested that certain electrical appliances and devices (such as fluorescent lighting ballast), which have PCB-containing components, can emit PCBs into the indoor air, thereby elevating indoor PCB levels significantly above outdoor background levels.

MONS 027361

8. ANALYTICAL METHODS

8.1 ENVIRONMENTAL MEDIA

The method widely used in laboratories for the analysis of PCBs in complex environmental samples is capillary column gas chromatography with electron capture (EC) detection (Schneider et al. 1984, Alford-Stevens et al. 1986). The use of mass spectrometry (MS) detectors has increased significantly, but most laboratories rely on EC detectors. EC detectors are more sensitive than MS detectors operated in electron ionization mode; the sensitivity difference can be as much as 2 or 3 orders of magnitude (Alford-Stevens et al. 1986). Table 8.1 lists several analytical methods, which have been standardized by either the EPA or NIOSH, for PCB analysis. Details of sample collection, storage, and analysis of PCBs are available (Erickson 1986).

The analytical methods referenced in Table 8.1 pertain to the detection of Aroclor formulations and not individual PCB isomers. With EPA Method 680, however, PCBs are identified and measured by the level of chlorination (EPA 1985c). This method has been used only since 1981, and most environmental data reported before that were probably underestimated.

The determination of Aroclor concentrations (rather than the level of chlorination) in environmental samples is complex and can produce significantly different results from different laboratories even though the analytical procedures have been standardized (Alford-Stevens et al. 1985). As a result of the difference in biodegradability, water solubility, and volatility of individual PCB isomers, the concentrations of these individual isomers in environmental samples can be strikingly different from the commercial PCB analytical reference standards.

8.2 BIOMEDICAL SAMPLES

Analytical methods used for biomedical samples are listed in Table 8.2. Gas chromatography-mass spectrometry procedures developed to determine milligram-per-kilogram levels of PCBs in breast milk and fat (Hutzinger et al. 1974) usually have lower sensitivity than EC detectors (Safe et al. 1985, Smrek and Needham 1982). No accepted quantitative procedure for the determination of the total PCB content in human tissue sample exists. The PCB standard mixture selected for quantification varies between investigators since no standard mixture exists with the same peak pattern as in human tissues because of differences in metabolism of the various PCB isomers. In recent years, high-resolution gas chromatography has made it possible to use single PCB congeners for quantitation. The selection of the congeners may be made on the basis of their abundance in the samples, their toxicity, or their availability in analytical standards. In general, if only 1 to 3 major peaks are selected,

MONS 027362

Table 8.1. Analytical methods for environmental media[a]

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy/precision	Reference
Air	Adsorption on glass fiber and Florisil; hexane desorption	GC/EC	0.0006 mg/m³ for 50-L sample	4.4% RSD (analytical) at concentrations <10 mg/m³	NIOSH 1984a [method No. 5503]
Air	Adsorption on Florisil; hexane desorption, perchlorination	GC/EC	0.01 mg/m³ (32 pg/injection)	2.8% RSD (analytical and perchlorination) at concentrations <10 mg/m³	NIOSH 1977a [method No. P & CAM 253]
Water	Extraction with methylene chloride; dry extract; exchange to hexane	GC/EC	0.065 µg/L (PCB-1242)	Standard deviation 1.6–5.5% and accuracy 88–96% at 25–110 µg/L	EPA 1982a [method 608]
Water	Extraction with methylene chloride	GC/MS	30–36 µg/L (PCB-1221, 1254)	Standard deviation 11–13% and accuracy 77–80% at 5–2000 µg/L	EPA 1982a [method 625]
Air	Adsorption on water-deactivated Florisil, hexane desorption; perchlorination with antimony pentachloride at 200°C	GC/EC	NR	NR	Liu and Que Hee 1985, 1987
Soil, sediments, and other solid sample matrices	Extraction with hexane-acetone mixture, Florisil column chromatographic clean-up and dechlorination by copper or mercury if necessary	GC/EC	<1 µg/g	NR	EPA 1983b [method 8080]

[a]GC = gas chromatography; EC = electron capture; MS = mass spectroscopy; RSD = relative standard deviation, NR = not reported.

MONS 027363

Table 8.2. Analytical methods for biological samples

Sample matrix	Sample preparation	Analytical method[a]	Detection limit	Accuracy/precision	References
Blood serum	Extract serum with ethyl ether and n-hexane; treat with methanolic KOH; extract with hexane and column chromatographic cleanup by silica gel	HRGC/EC	1.0 ng/mL on 10-mL sample	>80% accuracy at 25-400 ng/mL	NIOSH 1984b [method No. S004]
Tissue, eggs, fat	See Bush and Lo 1973	TLC	0.5 mg/kg	Precision ±0.05 mg/kg at 0.5 mg/kg	IARC 1978
Serum	Mixed solvent extraction, column chromatographic cleanup on silica gel	GC/EC	NR	Accuracy 92.6% at 50 μg/L and 114.1% at 10 μg/L; accuracy 89.6-136.1% at 9.9-74.2 μg/L for inter-laboratory determinations	Burse et al. 1983a,b
Serum	Solvent extraction, column chromatographic cleanup on 10% silver nitrate on silica gel	GC/EC	NR	Accuracy 93.7% at 41 μg/L	Needham et al. 1980
Serum	Mixed solvent extraction, column chromatographic cleanup with hydrated silica gel for separation of PCBs from PBBs	GC/EC	2.5 ng/mL	Accuracy 95.3% at 100 μg/L and 105-127% at 10 μg/L	Needham et al. 1981
Adipose tissue	Solvent extraction, column chromatographic cleanup on sulfuric acid/silica gel and 10% silver nitrate/silica gel columns	GC/EC	NR	Accuracy 91-93% at 3 μg/g	Sanvordeker and Needham 1982
Human milk	Mixed solvent extraction, cleanup on Florisil-silicic acid column	HRGC/EC	NR	NR	Mes et al. 1984
Serum	Solvent extraction with diethyl ether and hexane, sulfuric acid, and silica column cleanup	HRGC/EC	0.1 ng/mL	65% at 25-125 ng/mL	Lucianno et al. 1985
Blood	Solvent extraction with hexane, methanolic KOH hydrolysis, silica gel, and alumina column cleanup and perchlorination	GC/EC	NR	NR	Lin and Qua Hsu 1985, 1987

[a]HRGC = high-resolution gas chromatography; GC = gas chromatography; EC = electron capture; TLC = thin-layer chromatography; NR = not reported

MONS 027364

the results will be greater by a factor of approximately 2 than those obtained if a dozen peaks are selected. A congener-specific analysis of a commercial PCB preparation and the PCB composition of a human milk sample have been reported by Safe et al. (1985). Variables in sampling method may also greatly influence results. For example, PCB level in milk fat may decrease during lactation and with maternal age, weight, and purity (Jensen 1987). It has been shown by Lawton et al. (1985) that random error, interlaboratory variations in procedure, and methods used for reporting data can all have considerable impact on the reported PCB levels in human tissues. Such effects, however, should not deter investigators from using serum PCB data for assessing environmental exposure to populations or for statistical correlations with clinical parameters in epidemiological studies. Caution should be exercised when comparing exposure estimates or health effect studies reported by different investigators or when considering "the use of a specific serum PCB tolerance limit as a basis for administration action" (Lawton et al. 1985).

9. REGULATORY AND ADVISORY STATUS

9.1 INTERNATIONAL

No data were located in the available literature.

9.2 NATIONAL

9.2.1 Regulations

9.2.1.1 Food--FDA temporary tolerances

Agency	Standard	Value (ppm)	References
FDA	Foods	0.2-3.0	EPA 1987a
FDA	Packaging	10.0	EPA 1987a

9.2.2 Advisory Guidance

9.2.2.1 Air

AGENCY	ADVISORY
	PCBs
NIOSH	TLV-TWA--1.0 $\mu g/m^3$ (NIOSH 1977b)
National Academy of Sciences (NAS)	Suggested no adverse response level (SNARL)--350 $\mu g/L$ (NAS 1977)
	Aroclor 1254
American Conference of Government Industrial Hygienist (ACGIH)	TLV-TWA--0.5 mg/m^3 (ACGIH 1986)
	Aroclor 1242
ACGIH	TLV-TWA--1 mg/m^3 (ACGIH 1986)

9.2.2.2 Water

AGENCY	ADVISORY
EPA	Ambient water quality criteria (AWQC)--0.79 to 0.0079 ng/L for carcinogenicity at 10^{-5} to 10^{-7} risk levels (EPA 1980a) Drinking water criteria (DWC)--0.5 to 0.005 $\mu g/L$ for carcinogenicity at 10^{-4} to 10^{-6} risk levels (EPA 1987a)

MONS 027366

Aroclor 1016

EPA — Longer-term health advisory (HA) (adult)--0.0035 mg/L (EPA 1987a)
Longer-term HA (child)--0.001 mg/L (EPA 1987a)

9.2.2.3 Soil

AGENCY	ADVISORY
EPA	Permissible PCB soil contamination levels corresponding to: Noncancer 10-day HA (adult)--700 μg/day Noncancer 10-day HA (child)--100 μg/day Cancer risk specific doses: 1.75 to 0.00175 μg/day at 10^{-4} to 10^{-7} risk levels (EPA 1986d)

9.2.2.4 Others

AGENCY	ADVISORY
EPA	Reportable quantity (RQ) (statutory) - 10 lb (EPA 1985d) RQ (proposed) - 1 lb (EPA 1987d)

9.2.3 Data Analysis

Reference dose. The EPA (1987a) derived an oral reference dose (RfD) of 0.0001 mg/kg/day for Aroclor 1016 based on the study by Barsotti and Van Miller (1984) using an uncertainty factor of 100. This RfD was used to calculate longer-term HAs for adults and children. In this study, rhesus monkeys were maintained on diets containing Aroclor 1016 at 0.025, 0.25, and 1.0 ppm for approximately 7 months prior to mating and during gestation. The offspring of the 1.0-ppm group were significantly smaller than the controls. No effects were observed at 0.25 ppm, which was considered a NOAEL and is equivalent to a dose of 0.0105 mg/kg/day, assuming that a monkey consumes a daily amount of food equal to 4.2% of its body weight. The RfD was calculated according to methods outlined in Barnes et al. (1987) as follows:

$$RfD = (0.01 \text{ mg/kg/day})/(100) = 0.0001 \text{ mg/kg/day},$$

where: 0.01 mg/kg/day = NOAEL

100 = uncertainty factor for interspecies (10) and intraspecies (10) extrapolation, appropriate for use with an animal NOAEL.

Carcinogenic potency. EPA (1987a) determined that the positive evidence for carcinogenicity of Aroclor 1254, Aroclor 1260, Kanaclor 500, and Clophen A-30 and A-60 in animals, along with inadequate evidence in humans places these PCBs in category B2, probable human carcinogens. Because any PCB mixture that contains appreciable amounts of the components in Aroclors 1254 and 1260, Kanaclor 500, and Clophen A-30 and A-60 are likely to present a carcinogenic risk and because of the variety and variability of PCB mixtures, EPA (1987a) recommended that all commercial PCB mixtures be considered to have a similar carcinogenic potential and classified all PCB mixtures in category B2.

IARC (1982) has classified PCBs in Group 2B based on sufficient evidence in animals, inadequate evidence in humans and inadequate evidence for mutagenicity.

EPA (1987a) used the Norback and Weltman (1985) study as the basis for a quantitative carcinogenicity risk assessment for PCBs. The dietary level of 100 ppm Aroclor 1260 was converted to an intake of 5 mg/kg/day by assuming that a rat consumes food equal to 5% of its body weight per day. This dosage was converted to a TWA dosage of 3.45 mg/kg/day to reflect the fact that rats received 100 ppm for 16 months, 50 ppm for 8 months, and 0 ppm for the last 5 months. The rat dosage was converted to an equivalent human dose of 0.59 mg/kg/day on the basis of relative body surface areas. Incidences of trabecular carcinomas, adenocarcinomas, and neoplastic nodules in the liver were combined to produce total incidences of 45/47 in treated females and 1/49 in controls. Using these data, EPA (1987a) calculated a human q_1^* of 7.7 $(mg/kg/day)^{-1}$. Because there is no information regarding which constituents of any PCB mixture might be carcinogenic, Aroclor 1260 is assumed to be representative of other mixtures, and this potency estimate applies to them as well (EPA 1987a). The q_1^* was verified by the EPA agency-wide CRAVE committee on April 22, 1987 (EPA 1987e).

9.3 STATE

(Regulations and advisory guidance from the states were still being compiled at the time of printing.)

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Threshold limit values and biological exposure indices for 1986-1987. Cincinnati, OH: ACGIH.

Albro PW, Fishbein L. 1972. Intestinal absorption of polychlorinated biphenyls in rats. Bull Environ Contam Toxicol; 8:26. (Cited in EPA 1985a)

Alford-Stevens AL, Budde WL, Bellar TA. 1985. Interlaboratory study on determination of polychlorinated biphenyls in environmentally contaminated sediments. Anal Chem; 57: 2452-7.

Alford-Stevens AL, Bellar TA, Eichelberger JW, Budde WL. 1986. Accuracy and precision of determinations of chlorinated pesticides and polychlorinated biphenyls with automated interpretation of mass spectrometric data. Anal Chem; 58(9):2022-2029.

Allen JR. 1975. Response of the nonhuman primate to polychlorinated biphenyl exposure. Fed Proc; 34:1675-1679.

Allen JR, Abrahamson LJ. 1973. Morphological and biochemical changes in the liver of rats fed polychlorinated biphenyls. Arch Environ Contam Toxicol; 1:265-280. (Cited in EPA 1987a)

*Allen JR, Barsotti DA. 1976. The effects of transplacental and mammary movement of the PCBs on infant rhesus monkeys. Toxicology; 6:331.

Allen JR, Norback DH. 1973. Polychlorinated biphenyl and triphenyl induced gastric mucosal hyperplasia in primates. Science; 179:498.

Allen JR, Carstens LA, Barsotti DA. 1974a. Residual effects of short-term, low-level exposure of nonhuman primates to polychlorinated biphenyls. Toxicol Appl Pharmacol; 30:440-451.

Allen JR, Norback DH, Hsu IC. 1974b. Tissue modifications in monkeys as related to absorption distribution and excretion of polychlorinated biphenyls. Arch Environ Contam Toxicol; 2(1):86-95.

Allen JR, Cartens LA, Abrahamson LJ, Marlar RJ. 1975. Reponses of rats and non-human primates to 2,5,2',5'-tetrachlorobiphenyl. Environ Res; 9:265-273. (Cited in EPA 1987a)

*Key study

MONS 027369

*Allen JR, Barsotti DA, Lambrecht LK, Van Miller JP. 1979. Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann NY Acad Sci; 320:419.

*Allen JR, Barsotti DA, Carstens LA. 1980. Residual effects of polychlorinated biphenyls on adult nonhuman primates and their offspring. J Toxicol Environ Health; 6(1):55-66. (Cited in EPA 1987a)

Alvares AP, Kappas A. 1979. Lead and polychlorinated biphenyls: Effects on heme and drug metabolism. Drug Metab Rev; 10:91-106.

Alvares AP, Fischbein A, Anderson KE, Kappas A. 1977. Alterations in drug metabolism in workers exposed to polychlorinated biphenyls. Clin Pharmacol Ther; 22:140.

Amano M, Yagi K, Nakajima H, Takehara R, Sakai H, Umeda G. 1984. Statistical observations about the causes of death of patients with oil poisoning. Japan Hygiene; 39:1-5. (Cited in EPA 1987a)

Anderson HA. 1985. Utilization of adipose tissue biopsy in characterizing human halogenated hydrocarbon exposure. Environ Health Perspect; 60:127-131.

Anderson LM, Van Havere K, Budinger JM. 1983. Effects of polychlorinated biphenyls on lung and liver tumors initiated in suckling mice by *N*-nitrosodimethylamine. JNCI; 71(1):157-163. (Cited in EPA 1985a)

Ando M, Saito H, Wakisaka I. 1985. Transfer of polychlorinated biphenyls to newborn infants through the placenta and mothers' milk. Arch Environ Contam Toxicol; 14(1):51-7.

*Aulerich RJ, Ringer RK. 1977. Current status of PCB toxicity, including reproduction to mink. Arch Environ Contam Toxicol; 6:279.

Bahn AK, Rosenwaike I, Herrmann N, Grover P, Stellman J, O'Leary K. 1976. Melanoma after exposure to PCBs. New Eng J Med; 295:450.

Bahn AK, Grover P, Rosenwaike I, O'Leary K, Stellman J. 1977. PCB and melanoma. New Eng J Med; 296:108. (Cited in EPA 1987a)

Baker EL, Landrigan PJ, Glueck CJ, et al. 1980. Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am J Epidemiol; 112:553-563.

Baker JE, Eisenreich SJ, Johnson TC, Halfman BM. 1985. Chlorinated hydrocarbon cycling in the benthic nepheloid layer of Lake Superior. Environ Sci Technol; 19:854-61.

Bannister R, Davis D, Zacharewski T, Tizard I, Safe S. 1987. Aroclor 1254 as a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin antagonist: effects on enzyme induction and immunotoxicity. Toxicology (in press).

Barnes P, Bellin J, DeRosa C, et al. 1987. Reference Dose (RfD): Description and use in health risk assessments. Appendix A of the Integrated Risk Information System (IRIS). OHEA, ORD, Washington, DC. EPA 600/8-86-0321.

*Barsotti DA, Allen JR. 1975. Effects of polychlorinated biphenyls on reproduction in the primate. Fed Proc; 34:338.

*Barsotti DA, Van Miller JP. 1984. Accumulation of a commercial polychlorinated biphenyl mixture (Aroclor 1016) in adult rhesus monkeys and their nursing infants. Toxicology; 30(1):31-44.

*Barsotti DA, Merlar RJ, Allen JR. 1976. Reproductive dysfunction in rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmat Toxicol; 14:99-103.

Becker GM, McNulty WP, Bell M. 1979. Polychlorinated biphenyle-induces morphologic changes in the gastric mucosa of the rhesus monkey. Invest; 40:373.

Bell M. 1983. Intrastructural features of the murine cutaneous microvasculature after exposure to polychlorinated biphenyls compounds (PCBs) and benzo(a)pyrene (BAP). Virchows Arch B; 42(2):131-142. (Cited in EPA 1987a)

Benthe HF, Knop J, Schmoldt A. 1972. Absorption and distribution of polychlorinated biphenyls (PCB) after inhalatory application. Arch Toxicol; 29:85. (Cited in EPA 1985a)

Berry DL, DiGiovanni J, Juchau MR, Bracken WM, Gleason GL, Slaga TJ. 1978. Lack of tumor-promoting ability of certain environmental chemicals in a two-stage mouse skin tumorigenesis assay. Res Commun Chem Pathol Pharmacol; 20(1):101-108.

Bidleman TF. 1981. Interlaboratory analysis of high molecular weight organochlorines in ambient air. Atmos Environ; 15:619-24.

Biocca M, Gupta BNL, Chae K, McKinney JD, Moore JA. 1981. Toxicity of selected symmetrical hexachlorobiphenyl isomers in the mouse. Toxicol Appl Pharmacol; 58:461-474. (Cited in EPA 1987a).

Birnbaum LS, Weber H, Harris MW, Lamb JC, McKinney JD. 1985. Toxic interaction of specific polychlorinated biphenyls and 2,3,7,8-tatrachlorodibenzo-p-dioxin: increased incidence of cleft palate in mice. Toxicol Appl Pharmacol; 77:292-302.

Blazak WF, Marcum JB. 1975. Attempt to introduce chromosomal breakage in chicken embryos with Aroclor 1242. Poultry Sci; 54: 310. (Cited in Harbison, 1986)

*Bleavins MR, Aulerich RJ, Ringer RK. 1980. Polychlorinated biphenyls (Aroclors 1016 and 1242): Effects on survival and reproduction in mink and ferrets. Arch Environ Contam Toxicol; 9(5):627-635.

Bleavins MR, Breslin WJ, Aulerich RJ, Ringer RK. 1984. Placental and mammary transfer of a polychlorinated biphenyl mixture (Aroclor 1254) in the European ferret (*Mustela putorius furo*). Environ Toxicol Chem; 3(4):637-44.

Boon JP, Duinker JC. 1986. Monitoring of cyclic organochlorines in the marine environments. Environ Monit Assess; 7:189-208.

Bopp RF, Simpson HJ, Olsen CR, Trier RM, Kostyk N. 1982. Chlorinated hydrocarbons and radionuclids chronologies in sediments of the Hudson River and Esturary, NY. Environ Sci Technol; 16:666.

Brezner E, Terkel J, Perry AS. 1984. The effect of Aroclor 1254 (PCB) on the physiology of reproduction in the female rat--I. Comp Biochm Physiol; 77(1):65-70.

Brown DP, Jones M. 1981. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health; 36(3):120-129.

Brown JF, Jr, Lawton, RW. 1984. Polychlorinated biphenyl (PCB) partitioning between adipose tissue and serum. Bull Environ Contam Toxicol; 33:277-280.

Brown JF, Jr, Bedard BL, Brennan MJ, Carnahan JC, Feng H, Wagner RE. 1987. Polychlorinated biphenyl dechlorination in aquatic sediments. Science; 236:709-12.

Polychlorinated biphenyl dechlorination in aquatic sediments. Science; 236:709-12.

*Bruckner JV, Khanna KL, Cornish HH. 1973. Biological responses of the rat to polychlorinated biphenyls. Toxicol Appl Pharmacol; 24:434-448.

*Bruckner JV, Khanna KL, Cornish HH. 1974. Effect of prolonged ingestion of polychlorinated biphenyls on the rat. Food Cosmet Toxicol; 12:323.

Burkhard LP, Armstrong DE, Andren AW. 1985. Henry's law constants for the polychlorinated biphenyls. Environ Sci Technol; 19:590-6.

Burse VW, Needham LL, Korver MP et al. 1983a. Gas-liquid chromatographic determination of polychlorinated biphenyls and a selected number of chlorinated hydrocarbons in serum. J Assoc Off Anal Chem; 66:32-39.

Burse VW, Needham LL, Lapeza CR, Jr, et al. 1983b. Evaluation of potential analytical approach for determination of polychlorinated biphenyls in serum: Interlaboratory study. J Assoc Off Anal Chem; 66:956-968.

Bush B, Snow J, Koblintz. 1984. Polychlorobiphenyl (PCB) congeners, p,p'-DDE, and hexachlorobenzene in maternal and fetal cord blood from mothers in Upstate New York. Arch Environ Contam Toxicol; 13: 517-527.

Calabrese EJ, Sorenson AJ. 1977. The health effects of PCBs with particular emphasis on human high risk groups. Rev Environ Health; 2(4):285-304. (Cited in EPA 1987a)

Calandra JC. 1976. Summary of toxicological studies on commercial PCBs. In: Proceedings of the National Conference of Polychlorinated Biphenyls. EPA Report 560/6-75-004. (Cited in Harbison 1986)

Callahan MA, Slimak MW, Gabel NW, et al. 1979. Water-related environmental fate of 129 Priority Pollutants, Vol. I., Chapter 36. EPA 440/4-79-029a. Washington, DC: EPA.

Carey AE, Gowen JA, Tai H, Mitchell WG, Wiersma GB. 1979a. Pesticide residue levels in soils and crops from 37 states, 1972 - National Soils Monitoring Program (IV). Pestic Monit J; 12:209-29.

Carey AE, Douglas P, Tai H, Mitchell WG, Wiersma GB. 1979b. Pesticide residue concentrations in soils of five United States cities, 1971-Urban soils monitoring program. Pestic Monitor J; 13:17-22.

*Carter JW. 1985. Effects of dietary PCBs (Aroclor 1254) on serum levels of lipoprotein cholesterol in Fischer rats. Bull Environ Contam Toxicol; 34(3):427-431.

Chakraborty D, Bhattacharyya A, Chatterjee J, et al. 1978. Biochemical studies on polychlorinated biphenyls toxicity in rats: Manipulation by Vitamin C. Intern J Vit Nutr Res; 48:22. (Citad in EPA 1985a)

Chase KH, Wong O, Thomas D, Berney BW, Simon RK. 1982. Clinical and metabolic exposure to polychlorinated biphenyls (PCBs). J Occup Med; 24:109-114. (Cited in Kreiss 1985)

Chemline. 1987. On-line computer data base. National Library of Medicine. June 4, 1987.

Chen PH, Luo ML, Wong CK, Chen CJ. 1982. Comparative rates of elimination of some individual polychlorinated biphenyls from the blood of PCB-poisoned patients in Taiwan. Food Chem Toxicol; 20(4):417-425.

Chen PH, Wong CK, Rappe C, Nygren M. 1985. Polychlorinated biphenyls, dibenzofurans and quaterphanyls in toxic rice-bran oil and in the blood and tissues of patients with PCB poisoning (Yu-Cheng) in Taiwan. Environ Health Perspect; 29:475-678. (Cited in EPA 1987a)

Christensen ER, Lo CK. 1986. Polychlorinated biphenyls in dated sediments of Milwaukee Harbor, Wisconsin. Environ Pollut; 12:217-232.

Chu CK, Stella VJ, Bruckner JV, Jiang WD. 1977. Effects of long-term exposure to environmental levels of polychlorinated biphenyls on pharmacokinetics of pentobarbital in rats. J Pharm Sci; 66(2):238-241. (Cited in EPA 1987a)

*Collins WT, Capen CC. 1980a. Fine structural lesions and hormonal alterations in thyroid glands of perinatal rats exposed in utero and by milk to polychlorinated biphenyls. Am J Path; 99:125-142.

Collins WT, Capen CC. 1980b. Biliary excretion of thyroxine-I-125 and fine structural alterations in the thryoid glands of gunn-rats fed PCBs. Lab Invest; 43:158.

Collins WT, Capen CC. 1980c. Ultrastructural and functional alterations of the rat thyroid gland produced by polychlorinated biphenyls compared with iodide excess and deficiency, and thyrotropin and thyroxine administration. Virchos Arch B; 33(3):213-231.

Collins WT, Capen CC, Kasza L, Carter C, Dailey RE. 1977. Effect of polychlorinated biphenyl (PCB) on the thyroid gland of rats. Ultrastructural and biochemical investigations. Am J Pathol; 89:119.

Condon SK. 1983. (Commonwealth of Massachusetts Department of Public Health). Personal Communications, August 25 and 28, 1983. (Cited in Kreiss 1985)

Conolly RB, Szabo S, Jaeger RJ. 1979. Vinylidene fluoride. Acute hepatotoxicity in rats pretreated with PCB or phenobarbital. Proc Exp Biol Med; 162:163. (Cited in EPA 1985a)

Creaser CS, Fernandes AR. 1986. Background levels of polychlorinated biphenyls in British soils. Chemosphere; 15:499-508.

Davidorf FH, Knupp JA. 1979. Epidemiology of ocular melanoma. Incidence and geographic relationship in Ohio (1967-1977). Ohio State Med J; 75(9):561-564.

DiGiovanni J, Viaje A, Berry DL, Slaga TJ, Juchau MR. 1977. Tumor-initiating ability of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and Aroclor 1254 in the two-stage system of mouse skin carcinogenesis. Bull Environ Contam Toxicol; 18(5):552-557.

Dikshith TSS, Rockwood W, Abraham R, Coulston F. 1975. Effects of polychlorinated biphenyls (Aroclor 1254) on rat testis. Exp Mol Pathol; 22:376. (Cited in EPA 1987a)

Drill VA, Freiss SL, Hays HW, Loomis TA, Shaffer CB. 1981. Potential health effects in the human from exposure to polychlorinated biphenyls (PCBs) and related impurities. Unpublished Report, Arlington, VA: Drill, Freiss, Hays, Loomis and Shaffer, Inc.

Drotman DP, et al.** 1981. Human exposure to PCBs in southern Idaho. Internal Report EPA-79-105-2, Centers for Disease Control, Atlanta, November 2, 1981. (Cited in Kreiss 1985)

**No other names provided.

Drotman DP, Baxter, PJ, Liddle JA, Brokopp CD, Skinner MD. 1983. Contamination of the food chain by polychlorinated biphenyls from a broken transformer. Am J Publ Health; 73:290-292.

Duggan RE, Corneliussen PE, Duggan MB, McMahon BM, Martin RJ. 1983. Pesticide residue levels in foods in the United States from July 1, 1969 to June 30, 1976. Washington, DC: Food Drug Admin Div Chem Technol; 240 pp.

Durfee RL. 1976. Production and usage of PCBs in the United States. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004. Washington, DC: Environmental Protection Agency; p. 103-107.

Eduljee G, Badsha K, Price L. 1985. Environmental monitoring for PCB and heavy metals in the vicinity of a chemical waste disposal facility-I. Chemosphere; 14:1371-82.

Eduljee G, Badsha K, Scudamore N. 1986. Environmental monitoring for PCB and trace metals in the vicinity of a chemical waste disposal facility-II. Chemospere; 15:81-93.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol; 15:30-8.

Emmett EA. 1985. Polychlorinated biphenyl exposure and effects in transformer repair workers. Environ Health Persp; 60:185-192.

EPA. 1976. PCBs in the United States. Industrial Use and Environmental Distribution, PB-252 012. Springfield, VA: National Technical Information Service; p. 4-5, 34-35, 54-57, 198-210, 322-334. (Cited in IARC 1978)

EPA. 1979. Polychlorinated Biphenyls (PCBs); Proposed Rulemaking for PCB Manufacturing Exemptions. Federal Register; 44(106):31564-31567.

EPA. 1980a. Hazard waste generation and commercial hazardous waste management capacity: An assessment, SW-894. Washington, DC: EPA; p. D-4.

EPA. 1980b. Ambient water quality criteria for polychlorinated biphenyls. Washington, DC: EPA; EPA 440/5-80-068. NTIS PB81-117798.

EPA. 1982a. Test methods. Methods for organic chemical analysis of municipal and industrial wastewater. EPA 600/4-82-057. Cincinnati, OH: EPA; p. 608-1 - 608-11; 625-1 - 625-12.

EPA. 1982b. Test methods for evaluating solid waste. Washington, DC: SW-846, Office of Solid Waste and Emergency Response, EPA; p. 8080-1 8080-17.

EPA. 1985a. Drinking water criteria document for polychlorinated biphenyls (PCBs). Draft. Washington, DC: ODW; NTIS PB 86-118312/AS.

EPA. 1985b. Health assessment document for polychlorinated dibenzo-*p*-dioxins. EPA/600/8-84/014F. p. II-1 - II-29; IV-1 - IV-37.

EPA. 1985c. Method 680, Determination of pesticides and PCBs in water and soil/sediment by gas chromatography/mass spectrometry. Cincinnati, OH: Environmental Monitoring and Support Laboratory, Office of Research and Development, EPA. (Cited in Alford-Stevens 1986)

EPA. 1985d. Notification requirements, reportable quantity adjustments, final rule and proposed rule. Fed Reg; 50(65):13456-13523.

EPA. 1985e. Baseline estimates and time trends for beta-benzene hexachloride, hexachlorobenzene, and polychlorinated biphenyls in human adipose tissue 1970-1983. Washington, DC: OTS, Exposure Evaluation Division. EPA 560/5-85-025. Document No. NHATS-SS-01.

EPA. 1986a. Reference values for risk assessment. First Draft. ECAO-CIN-477. Cincinnati, OH: Environmental Criteria and Assessment Office.

EPA. 1986b. Broad scan analysis of the FY 82 national human adipose tissue survey specimens. Volume III - Semi-volatile organic compounds. OTS, Washington, DC. EPA-560/5-86-037.

EPA. 1986c. Guidelines for Carcinogen Risk Assessment. Fed Reg; 51(185):33992-34003.

EPA. 1986d. Development of advisory levels for polychlorinated biphenyls (PCBs) cleanup. Final. Washington, DC: Office of Emergency and Remedial Response. OHEA-E-187.

EPA. 1987a. Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs). ECAO-CIN-414. Final.

EPA. 1987b. Polychlorinated biphenyl spills cleanup policy; final rule. Fed Reg; 52(63):10688-10710.

EPA. 1987c. Graphical Exposure Modeling System (GEMS). Personal computer version April, 1987. Research Triangle Park, NC: EPA.

EPA. 1987d. Reportable quantity adjustments. Proposed rule. Fed Reg; 52(50):8140.

EPA. 1987e. IRIS (Integrated Risk Information System), CRAVE (Carcinogen Risk Assessment Validation Endeavor) for polychlorinated biphenyls. (Verification date: 4/22/87). Online: input pending. Cincinnati, OH: OHEA, ECAO.

EPA-NIH (National Institute of Health). 1987. OHM-TADS (Oil and Hazardous Materials Technical Assistance Data System). On-line: 1987. EPA-NIH, Washington, DC.

Erickson, MD. 1986. Analytical chemistry of PCBs. Stonsham, MA: Butterworth Publishers; p. 55-338.

MONS 027376

Fein GG. 1984. Intrauterine exposure of humans to PCBs: newborn effects. Duluth, MN: EPA. EPA-600/53-84-060. PB-84-186-887.

Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. 1984. Prenatal exposure to polychlorinated byphenyls - effects on birth size and bastational age. J Pediatrics; 105:315-320.

Felt GR, Mueller WF, Iatropoulos MJ, Coulston F, Korte F. 1977. Chronic toxicity of 2,5,4'-trichlorobiphenyl in young rhesus monkeys. I. Body distribution elimination and metabolism. Toxicol Appl Pharmacol; 41(3):619-627. (Cited in EPA 1987a)

Feltz HR. 1980. Significance of bottom material data in evaluation water quality. In: Contam Sed Fate Transport Case Studies Model Tox. Ann Arbor, MI: Ann Arbor Science; 1:271-87.

Finklea J, Priester LE, Creason JP, Haueer T, Hinners T, Hammer D. 1972. I. Polychlorinated biphenyl residues in human plasma expose a major urban pollution problem. Am J Publ Health; 62:645-651. (Cited in Kreiss 1985)

Fischbein A. 1985. Liver function tests in workers with occupational exposure to polychlorinated biphenyls (PCBs): Comparison with Yusho and Yu-Cheng. Environ Health Persp; 60:145-150.

*Fischbein A, Wolff MS, Lilis R, Thornton J, Selikoff IJ. 1979. Clinical findings among PCB-exposed capacitor manufacturing workers. Ann NY Acad Sci; 320:703-715.

Fischbein A, Wolff MS, Bernstein, Selikoff IJ. 1982. Dermatological findings in capacitor manufacturing workers exposed to dielectric fluids containing polychlorinated biphenyls. Arch Environ Health; 37:69-74.

Fischbein A, Rizzo JN, Solomon SJ, Wolff MS. 1985. Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls. Br J Ind Med; 42(6):426-430.

*Fishbein L. 1974. Toxicity of chlorinated biphenyls. Ann Rev Pharmacol; 14:139-156.

Frank R, Braun HE, Van Hoveholdrinet M, Sirons GJ, Ripley BD. 1982. Agriculture and water quality in the Canadian Great Lakes Basin: V. Pesticide use in 11 agricultural watersheds and presence in steam water, 1975-77. J Environ Qual; 11:497.

Gage JC, Holm S. 1976. The influence of molecular structure on the retention and excretion of polychlorinated biphenyls by the mouse. Toxicol Appl Pharmacol; 36:555-560.

Garthoff LH, Friedman L, Farber TM, et al. 1977. Biochemical and cytogenetic effects in rats caused by short-term ingestion of Aroclor 1254 or Firemaster BP6. J Toxicol Environ Health; 3:769. (Cited in EPA 1987a)

*Garthoff LH, Cerra FE, Marks EM. 1981. Blood chemistry alteration in rats after single and multiple gavage administration of polychlorinated biphenyls. Toxicol Appl Pharmacol; 60(1):33-44.

Gartner LM, Arias IM. 1966. Studies of prolonged neonatal jaundice in the breast-fed infant. J Pediat; 68(1):54. (Cited in EPA 1987a)

Gartrell MJ, Craun JC, Podrebarac DS, Gunderson EL. 1985a. Pesticides, selected elements, and other chemicals in adult total diet samples October 1979 - September 1980. J Assoc Off Anal Chem; 68:1184-97.

Gartrell MJ Craun JC, Podrebarac DS, Gunderson EL. 1985b. Pesticides, selected elements, and other chemicals in adult total diet samples October 1979 - September 1980. J Assoc Off Anal Chem; 68:862-73.

Gartrell MJ, Craun JC, Podrebarac DS, Gunderson EL. 1985c. Pesticides, selected elements, and other chemicals in infant and toddler diet samples, October 1979 - September 1980. J Assoc Off Anal Chem; 68:1163-83.

Gartrell MJ Craun JC, Podrebarac DS, Gunderson EL. 1986a. Pesticides, selected elements, and other chemicals in adult total diet samples October 1980 - March 1982. J Assoc Off Anal Chem; 69:146-61.

Gartrell MJ Craun JC, Podrebarac DS, Gunderson EL. 1986b. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples October 1980 - March 1982. J Assoc Off Anal Chem; 69:123-45.

Giam CS, Chan HS, Neff GS, Atlas EL. 1978. Phthalate ester plasticizers: A new class of marine pollutant. Science; 199:419-21.

Gillette JR. 1967. Individually different responses to drugs according to age, sex and functional or pathological state. In: Wolstenhome G, Proter R, eds. Drug Responses in Man. London: Churchill; p. 28. (Cited in EPA 1987a)

Goldstein JA, et al.** 1974. Experimental hepatic porphyria induced by polychlorinated biphenyls. Toxicol Appl Pharmacol; 27:437-448. (Cited in Drill et al. 1981)

Goto M, Sugiura K, Hattori M, Miyagawa T, Okamura M. 1974. Metabolism of 2,3-dichlorobiphenyl-^{14}C and 2,4,6-trichlorobiphenyl-^{14}C in the rat. Chemosphere; 5:227-232. (Cited in EPA 1987a)

Grant DL, Phillips WEJ. 1974. The effect of age and sex on the toxicity of Aroclor 1254, a polychlorinated biphenyl, in the rat. Bull Contam Toxicol; 12:145-152. (Cited in EPA 1987a)

Green S, Carr JV, Palmer KA, Oswald EJ. 1975a. Lack of cytogenetic effects in bone marrow and spermatogonial cells in rats treated with polychlorinated biphenyls (Aroclors 1242 and 1254). Bull Environ Contam Toxicol; 13:14-22.

Green S, Sauro FM, Friedman L. 1975b. Lack of dominant lethality in rats treated with polychlorinated biphenyls (Aroclor 1242 and 1254). Food Cosmet Toxicol; 13:507-510.

Griffin RA, Chou SFJ. 1981. Movement of PCBs and other persistent compounds through soil. Water Sci Technol; 13:1153-63.

Gustavsson P, Hogstedt C, Rappe C. 1986. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls. Am J Ind Med; 10:341-344.

*Haake JM, Safe S, Mayura K, Phillips TD. 1987. Aroclor 1254 as an antagonist of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicology Lett (in press).

Hansch C, Leo AJ. 1985. Medchem Project. Issue No. 26. Claremont, CA; Pomona College.

Harbison RD. 1986. Genotoxic effects of PCBs. Draft report sent to Dr. John Craddock. St. Louis, MO: Monsanto Chem.

Hashimoto K, Akasaka S, Takagi Y, et al. 1976. Distribution and excretion of [^{14}C]polychlorinated biphenyls after their prolonged administration to male rats. Toxicol Appl Pharmacol; 37:415-423.

Hatton RE. 1979. Chlorinated biphenyls and related compounds. In: Grayson M, Eckroth D, eds. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, New York, NY: John Wiley and Sons; p. 844-848.

Hattula ML. 1985. Mutagenicity of PCBs and their pyroaynthetic derivatives in cell-mediated assay. Environ Health Perspect; 60:255-257.

Heddle JA, Bruce WR. 1977. Comparison of tests for mutagenicity or carcinogenicity using assays for sperm abnormalities, formation of micronuclei and mutations in *Salmonella*. In: Hiatt HH, et al., ed. Origins of Human Cancer. Cold Spring Harbor Conf Cell Prolif. Cold Spring Harbor, NY: Cold Spring Harbor Lab; 4:1549. (Cited in EPA 1987a)

Hsit M, Klusek C, Baron J. 1984. Evidence of deposition of anthropogenic pollutants in remote Rocky Mountain lakes. Water Air Soil Pollut; 22:403-16.

Hill RH, Jr. 1985. Effects of polyhalogenated aromatic compounds on porphyrin metabolism. Environ Health Perspect; 60:139-143.

Hollifield HC. 1979. Rapid nephelometric estimate of water solubility of highly insoluble organic chemicals of environmental interest. Bull Environ Contam Toxicol; 23:579-86.

Hoopingarner R, et al.** 1972. Polychlorinated biphenyl interactions with tissue culture cells. Environ Health Perspect; 1:155. (Cited in Harbison, 1986)

*Hornshaw TC, Safronoff J, Ringer RK, Aulerich RJ. 1986. LC_{50} test results in polychlorinated biphenyl-fed mink: Age, season and diet comparisons. Arch Environ Contam Toxicol; 15(6):717-723.

HSDB (Hazardous Substances Data Bank). 1987. On-line computer data base. National Library of Medicine. June 4, 1987.

Hubbard HL. 1964. Chlorinated biphenyl and related products. In: Standen A, ed. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., Vol. 5, New York, NY: John Wiley and Sons; p. 291.

Humphrey HEB. 1976. Evaluation of changes of the level of polychlorinated biphenyls (PCB) in human tissue. Final Report on FDA Contract 223-73-2209. Lansing, Michigan: Michigan Department of Public Health.

Humphrey HEB. 1983a. Population studies of PCBs in Michigan residents. In: PCBs: Human and Environmental Hazards. D'Itri FM, Kamrin MA, eds. Ann Arbor, MI: Ann Arbor Science Publications. p. 299-310. (Cited in Kreise 1985)

Humphrey HEB. 1983b. Evaluation of humans exposed to waterborne chemicals of the Great Lakes. Final report for EPA Co-operative Agreement (CR807192). (Cited in Kreise 1985)

Hutton JJ, Meier J, Hackney C. 1979. Comparison of the in vitro mutagenicity and metabolism of dimethylnitrosamine and benzo[a]pyrene in tissues from inbred mice treated with phenobarbitol, 3-methylcholanthrene or polychlorinated biphenyls. Mutat Res; 66:75. (Cited in EPA 1985a)

Hutzinger S, Safe S, Zitko V. 1974. The chemistry of PCBs. Cleveland, OH: Chemical Rubber Publishing Co. (Cited in Callahan et al. 1979, IARC 1978)

Istapoulos MJ, Bailey J, Adams HP, Coulston, Hobson W. 1978. Response of nursing infant rhesus to clophen A-30 or hexachlorobenzene given to their lactating mothers. Environ Res; 16(1-3):38-47. (Cited in EPA 1987a)

IARC (International Agency for Research on Cancer). 1978. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Polychlorinated biphenyls and polybrominated biphenyls. IARC, vol. 18. Lyon, France: WHO.

IARC (International Agency for Research on Cancer). 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4. Lyon, France: WHO.

Ito N, Nagasaki H, Makiura S, Arai M. 1974. Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann; 66:545-549. (Cited in EPA 1985a)

Jacobson JL, Jacobson SW, Schwartz PM, Fein GG, Dowler JK. 1984a. Prenatal exposure to an environmental toxic: A test of the multiple effects model. Dev Psych; 20: 523-532.

Jacobson JL, Gein GG, Jacobson SW, et al. 1984b. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. Am J Public Health; 74(4):378-379.

Jacobson Sw, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. 1985. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev; 56:856-860.

Jaffe R, Stemmler EA, Eitzer BD, Hites RA. 1985. Anthropogenic, polyhalogenated, organic compounds in sedentary fish from Lake Huron and Lake Superior tributaries and embayments. J Great Lakes Res; 11:156-62.

Jensen S, Sundstrom G. 1974. Structures and levels of most chlorobiphenyls in the technical PCB products and in human adipose tissue. Ambio; 3:70-76. (Cited in EPA 1987a)

Jelinek CF, Corneliussen PE. 1976. Levels of PCBs in the U.S. food supply. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004. Washington, DC: Environmental Protection Agency; p. 147-154.

Jensen AA. 1987. Polychlorobiphenyls (PCBs), polychlorodibenzo-*p*-dioxins (PCDDs) and polychlorodibenzofurans (PCDFs) in human milk, blood, and adipose tissue. Sci Total Environ; 64:259-293.

Kasza L, Collins WT, Capen CC, Garthoff LH, Friedman L. 1978. Comparative toxicity of polychlorinated biphenyls and polybrominated biphenyl in the rat thyroid gland: Light and electron microscopic alterations after subacute dietary exposure. J Environ Pathol Toxicol; May-June(5): 587-599.

Kato N, Kawai K, Yoshida A. 1981. Effect of dietary level of ascorbic acid on the growth, hepatic lipid peroxidation, and serum lipids in guinea pigs fed polychlorinated biphenyls, Aroclor 1254. Bull Environ Contam Toxicol; 18:243. (Cited in EPA 1985a)

Keplinger ML, et al.** 1971. Toxicological studies with polychlorinated biphenyls. Toxicol Appl Pharmacol; 53:389. (Cited in Harbison 1986)

Kim NK, Stone DW. n.d. Organic chemicals and drinking water. NYS Dept Health; p. 101.

Kimbrough RD. 1987a. Human health effect of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Ann Rev Pharm Toxicol; 27:87.

Kimbrough RD. 1987b. Toxicology of halogenated biphenyls, dibenzodioxins, and dibenzofurans. ISI Atlas of Sciences: Pharmacology; 1:139-142.

Kimbrough RD, Linder RE. 1974. Induction of adenofibrosis and hepatomas in the liver of Balb/CJ mice by polychlorinated biphenyls (Aroclor 1254). JNCI; 53:547. (Cited in EPA 1987a)

Kimbrough RD, Linder RE, Gaines TB. 1972. Morphological changes in livers of rats fed polychlorinated biphenyls. Arch Environ Health; 25:354.

Kimbrough RD, Squire TA, Linder RE, Strandberg JD, Montali RJ, Burse VW. 1975. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. JNCI; 55:1453-1459.

Kimura NT, Baba T. 1973. Neoplastic changes in the rat liver induced by polychlorinated biphenyls. Gann; 64:105. (Cited in EPA 1985a)

Kleinert JJ. 1976. Sources of polychlorinated biphenyls in Wisconsin. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004. Washington, DC: Environmental Protection Agency; p. 124-6.

Kokoszka L, Flood J. 1985. A guide to EPA-approved PCB disposal methods. Chem Eng; 92(14):41-43.

Koller LD. 1977. Enhanced polychlorinated biphenyls lesions in Moloney leukemia virus-infected mice. Clin Toxicol; 11(1):107-116.

Kraul I, Karlog O. 1976. Persistent organochlorinated compounds in human organs collected in Denmark 1972-73. Acta Pharmacol Toxicol (Kbh); 38(2):38-73. (Cited in EPA 1985a)

Kreiss K. 1985. Studies on populations exposed to polychlorinated biphenyls. Environ Health Perspect; 60:193-199.

Kreiss K, Zack MM, Kimbrough RD, Needham LL, Smrek AL, Jones BT. 1981. Association of blood pressure and polychlorinated biphanyl levels. JAMA; 245(24):2505-2509.

Kreiss K, Roberts G, Humphrey HEB. 1982. Serial PBB levels, PCB levels, and clinical chemistries in Michigan's PBB cohort. Arch Environ Health; 37:141-147. (Cited in Kreiss 1985)

Kurechi M. 1983. A new sulfur-containing derivative and possibility of conjugate formation of PCBs in mice or rats. Agric Biol Chem; 47(6):1183-1191.

Kurechi M, Mio T. 1983a. On fluctuation of PCBs under various unnatural conditions in mice. Agric Biol Chem; 47(6):1173-1181.

Kurachi M, Mio T. 1983b. Studies on excretion and accumulation of PCBs in connection with their partial metabolism in the animal body. Part III. On the formation of a conjugate of PCBs with glutathione and its further metabolism in mice or rats. Agric Biol Chem; 47(6):1193-1199.

Kuratsune M., Shapiro, R. 1984. PCB poisoning in Japan and Taiwan. Am. J. Ind. Med; 5:1-153.

Kuratsune M. 1986. Letter to A Chiu and D Bayliss. Carcinogen Assessment Group, Washington, DC: EPA. June 30. (Cited in EPA 1987a)

Larsson P. 1985. Contaminated sediments of lakes and oceans act as sources of chlorinated hydrocarbons for release to water and atmosphere. Nature; 317:347-349.

Lawton RW, Brown JF, Ross Mr, Feingold J. 1982. Comperability and precision of serum PCB measurements. Arch Environ Health; 40: 29-37.

Lawton RW, Ross MR, Feingold J, Brown, Jr, JF. 1985. Effects of PCB exposure on biochemical and hematological finding in capacitor workers. Environ Health Perspect; 60:165-184.

Leifer A, Brink RH, Thom GC, Partymiller KG. 1983. Environmental transport and transformation of polychlorinated biphenyls. EPA-560/5-83-025. Washington, DC: Office of Pest Tox Sub; 206 pp. NTIS No. PB84-142579.

Lester R, Schmid R. 1964. Bilirubin metabolism. New Engl J Med; 270(15):779. (Cited in EPA 1985a)

Letz G. 1983. The toxicology of PCB's - an overview for clinicians. The Western J Med; 138:534-540.

Lewis RG, Martin BE, Sgontz DL, Howes JE, Jr. 1985. Measurements of fugitive atmospheric emissions of polychlorinated biphenyls from hazardous waste landfills. Environ Sci Technol; 19:986-91.

Lin JM, Que Hee SS. 1985. Optimization of perchlorination conditions for some representative polychlorinated biphenyls. Anal Chem; 57:2130-2134.

Lin JM, Que Hee SS. 1987. Change in chromatogram patterns after volatilization of some aroclors, and the associated quantitation problems. Am Ind Hyg Assoc J; 48:599-607.

*Linder RE, Gaines TB, Kimbrough RD. 1974. The effect of PCB on rat reproduction. Food Cosmet Toxicol; 12:63.

*Litterst CL, Farber TM, Baker AM, van Loon EJ. 1972. Effect of polychlorinated biphenyls on hepatic microsomal enzymes in the rat. Toxicol Appl Pharmacol; 23:112-122.

Lokietz H, Dowben RM, Hsia DY. 1963. Studies on the effect of Novobiocin and glucuronyl transferase. Pediatrics; 32:47. (Cited in EPA 1985a)

Loose LD, Pittman KA, Benitz KF, Silkworth JB, Mueller W, Coulston F. 1978a. Environmental chemical-induced immune dysfunction. Ecotoxicol Environ Safety; 2:173.

Loose LD, Silkworth JB, Pittman KA, Benitz KF, Mueller W,. 1978b. Impaired host resistance to endotoxic and malaria in polychlorinated biphenyl and hexachlorobenzene-treated mice. Inf Immun; 20(1):30.

Luotamo M, Jrvisalo, Aitio A. 1985. Analysis of polychlorinated biphenyls (PCBs) in human serum. Environ Health Persp; 60:327-332.

Lyman WJ, Reehl WF, Rosenblatt DH. 1982. Handbook of Chemical Property Estimation Methods. New York: McGraw-Hill Book Co.; p. 15-16.

Mabey WR, Smith JH, Podoll RT, et al. 1981. Aquatic fate process data for organic priority pollutants. EPA Report No. 440/4-81-014. Washington DC: EPA, Monitoring and Data Support Division, Office of Water Regulations and Standards; p. 115-128.

MacLeod KE. 1981. Polychlorinated biphenyls in indoor air. Environ Sci Technol; 15:926-8.

Makiura S, Aoe H, Sugihara S, Hirao K, Arai M, Ito N. 1974. Inhibitory effect of polychlorinated biphenyls on liver tumorigenesis in rats treated with 3'-methyl-4-dimethylaminoazobenzene, *N*-2-fluorenylacetamide, and diethylnitrosamine. JNCI; 53:1253-1257. (Cited in IARC 1978)

Maroni N, Columbi A, Arbosti G, Cantoni S, Foa V. 1981a. Occupational exposure to polychlorinated biphenyls in electrical workers. II. Health effects. Br J Ind Med; 38:55-60.

Maroni N, Columbi A, Cantoni S, Ferioli E, Foa V. 1981b. Occupational exposure to polychlorinated biphenyls in electrical workers. I. Environmental and blood polychlorinated biphenyls concentrations. Br J Ind Med; 38:49-54.

Masuda Y, Kagawa R, Kuroki H, Tokudom S, Kuratsune M. 1979. Transfer of various polychlorinated biphenyls to the fetuses and offspring of mice. Food Cosmet Toxicol; 17(6):623-627. (Cited in EPA 1987a)

Mazurek MA, Simoneit BRT. 1985. Organic components in bulk and wet-only precipitation. CRC Crit Rev Environ Control; 16:41-47. (Cited in EPA 1987a)

McConnell EE, Kinney JD. 1978. Exquisite toxicity in the guinea pig to structurally-similar halogenated dioxins, furans, biphenyls and naphthalenes. Toxicol Appl Pharmacol; 45:298. (Cited in EPA 1987a)

McNulty WP, Becker GM, Cory HT. 1980. Chronic toxicity of 3,3'4,4'- and 2,2'5,5'-tetrachlorobiphenyls in rhesus macques. Toxicol Appl Pharmacol; 56(2):182-190. (Cited in EPA 1985a)

MONS 027384

Meigs, JW, Albom JJ, Kartin Bl. 1954. Chloracne from an unusual exposure to Arochlor. JAMA; 154:1417-1418.

Mes J, Doyle JA, Adam BR, Davies DJ, Turton D. 1984. Polychlorinated biphenyls and organochlorine pesticides in milk and blood of Canadian women during lactation. Arch Environ Contam Toxicol; 13:217-223.

Misure JP, Hicks O, Kaley RG, Saeger VW. 1976. Characterization of polychlorinated biphenyls. In: National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004. Washington, DC: Environmental Protection Agency; p. 84-93.

Miller JW. 1944. Pathologic changes in animals exposed to a commercial chlorinated diphenyl. Pub Health Rep; 59:1085. (Cited in EPA 1985a)

Miller JW. 1985. Congenital PCB poisoning: a reevaluation. Environ Health Perspect; 60:211-214.

Mizutani T, Hidaka K, Matsumoto M. 1977. A comparative study on accumulation and elimination of tetrachlorobiphenyl isomers in mice. Bull Environ Contam Toxicol; 18:454. (Cited in EPA 1987a)

Monsanto. 1974. PCBs-Aroclors Tech Bull. O/PL 306A. St. Louis, MO. (Cited in Callahan et al. 1979)

Morgan RW, Ward JM, Hartman PE. 1981. Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats. Cancer Res; 41:5052-5059.

Morselli L, Brocco D, Pirni A. 1985. The presance of polychlorodibenzo-p-dioxins (PCDDs), polychlorodibenzofurans (PCDFs), and polychlorobiphenyls (PCBs) in fly ashes from various municipal incinerators under different technological and working conditions. Ann Chim; 75:59-64.

Muehlebach S, Bickel MH. 1981. Pharmacokinetics in rats of 2,4,5,2',4',5'-hexachlorobiphenyl, an unmetabolizable lipophilic model compound. Xenobiotica; 11(4):249-257. (Cited in EPA 1987a)

Murphy TJ, Formanski LJ, Brownawell B, Meyer JA. 1985. Polychlorinated biphenyl emissions to the atmosphere in the Great Lakes region. Municipal land fills and incinerators. Environ Sci Technol; 19(10):924-946.

Murray HE, Ray LE, Giam CS. 1981. Phthalic acid esters, total DDT and polychlorinated biphenyls in marine samples from Galveston Bay, Texas. Bull Environ Contam Toxicol; 26:769-74.

Nagasaki H, Tomii S, Mega T. 1975. Factors affecting induction of liver cancer by BHC and PCBs in mice. Abstract No. 235. Jpn J Hyg; 30:134. (Cited in IARC 1978)

NAS (National Academy of Sciences). 1977. Drinking water and health. Washington, DC: National Academy Press. (Cited in EPA 1987a)

NCI (National Cancer Institute). 1978. Bioassay of Aroclor 1254 for possible carcinogenicity. NCI-GC-TR-38. Bethesada, MD: National Cancer Institute. NTIS PB279624.

Needham LL, Amrek AL, Head SL, Burse VW and Liddle JA. 1980. Column chromatography separation of polychlorinated biphenyls from dichlorodiphenyltrichloroethane and metabolites. Anal Chem; 52:2227-2229.

Needham LL, Burse VW, Price HA. 1981. Temperature-programmed gas chromatographic determination of polychlorinated and polybrominated biphenyls in serum. J Assoc Off Anal Chem; 64:1131-1137.

Nelson NN, Hammon PB, Nisbet ICT, Sarofim AF, Drury WH. 1972. Polychlorinated biphenyls - environmental impact. Environ Res; 5:249-362. (Cited in EPA 1987a)

Nilsson B, Ramel C. 1974. Genetic tests on *Drosophila melanogaster* with polychlorinated biphenyls (PCB). Hereditas; 77:319-322. (Cited in EPA 1987a)

NIOSH (National Institute for Occupational Safety and Health). 1977a. NIOSH manual of analytical methods. 2nd ed. Taylor DG, ed. Vol. 1. Cincinnati, OH: U.S. Department of Health and Human Services, NIOSH; 244-1 - 253-7.

NIOSH (National Institute for Occupational Safety and Health). 1977b. Criteria for a recommended standard. Occupational exposure to polychlorinated biphenyls (PCBs). Rockville, MD: U.S. DHEW, PHS, CDC. NIOSH Publ. No. 77-225.

NIOSH (National Institute for Occupational Safety and Health). 1984a. NIOSH manual of analytical methods. 3rd ed. Eller PM, ed. Vol. 2. Cincinnati, OH: U.S. Department of Health and Human Services, NIOSH; p. 5503-1 - 5503-5.

NIOSH (National Institute for Occupational Safety and Health). 1984b. NIOSH manual of analytical methods. 3rd ed. Eller PM, ed. Vol. 1. Cincinnati, OH: U.S. Department of Health and Human Services, NIOSH; p. 8004-1 - 8004-4.

Nishizumi M. 1976. Radioautographic evidence for adsorption of polychlorinated biphenyls through the skin. Ind Health; 14:41-44.

*Norback DH, Weltman RH. 1985. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ Health Perspect; 60;97-105.

Norback DH, Mack E, Blomquist KA, Allen JR. 1978. Metabolic study of 2,4,5,2',4',5'-hexachlorobiphenyl in rhesus monkeys. Toxicol Appl Pharmacol; 45:331. (Cited in EPA 1985a)

NTIS (National Technical Information Service). 1987. Federal research in progress: On-line database.

Nyhan WL. 1961. Toxicity of drugs in the neonatal period. J Pediat; 59(1):1. (Cited in EPA 1987a)

Oatman L, Roy R. 1986. Surface and indoor air levels of polychlorinated biphenyls in public buildings. Bull Environ Contam Toxicol; 37:461-6.

Oesterle D, Deml E. 1983. Promoting effect of polychlorinated biphenyls on development of enzyme-altered islands in livers of weanling and adult rats. J Cancer Res Clin Oncol; 105(2):141-146. (Cited in EPA 1985a)

Orris P, Kominsky JR, Hryhorczyk D, Melius J. 1986. Exposure to polychlorinated biphenyls from an overheated transformer. Chemosphere; 15:1305-11.

Ouw HK, Simpson GR, Siyali DS. 1976. Use and health effects of Aroclor 1242, a polychlorinated biphenyl in an electrical industry. Arch Environ Health; 31:189.

Paris DF, Steen WC, Baughman GL. 1978. Role of the physicochemical properties of Aroclor 1016 and 1242 in determining their fate and transport in aquatic environments. Chemosphere; 7(4):319-325. (Cited in Callahan et al. 1979)

Parkinson A, Thomas PE, Ryan DE, et al. 1983. Differential time course of induction of rat liver microsomal cytochrom P-450 isozymes and epoxide hydrolase by Aroclor 1254. Arch Biochem Biophys; 225:203-215. (Cited in EPA 1987a)

Peakall DB, Lincer JL, Bloom SE. 1972. Embryonic mortality and chromosomal alterations caused by Aroclor 1254 in ring doves. Environ Health Perspect; 1:103-104. (Cited in EPA 1987a)

Pereira MA, Herren SL, Britt AL, Khoury MM. 1982. Promotion by polychlorinated biphenyls of enzyme-altered foci in rat liver. Cancer Lett; 15(2):185-190. (Cited in EPA 1985a)

Ray LE, Murray HE, Giam CS. 1983. Organic pollutants in marine samples from Portland, Maine. Chemosphere; 12:1031-8.

Reid D, Fox JM. 1982. Polychlorinated biphenyl report, Old Forge, Lackawanna County, Pennsylvania Department of Health, Division of Environmental Health, April 1982. (Cited in Kreiss 1985)

Requejo AG, West RH, Hatcher PG, McGillivary PA. 1979. Polychlorinated biphenyls and chlorinated pesticides in soils of the Everglades national park and adjacent agricultural areas. Environ Sci Technol; 13:931-6.

*Ringer RK, Aulerich RJ, Bleavins MR. 1981. Biological effects of PCBs and PBBs on mink and ferrets: a review. In: Khan MAQ, ed. Halogenated Hydrocarbons: Health and Ecological Effects. Elmsford NY: Permagon Press; p. 329-343. (Cited in Hornshaw et al. 1986).

Rodgers PW, Swain WR. 1983. Analysis of polychlorinated biphenyl (PCB) loading trends in Lake Michigan. J Great Lakes Res; 9:548-58.

Rogan WJ, Gladen BC, McKinney JD, et al. 1986. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr; 109:335-341.

Ryan JJ, Lau PY, Pilon JC, Lewis D, McLeod HA, Gervais A. 1984. Incidence and levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Lake Ontario commercial fish. Environ Sci Technol; 18:719-21.

Safe S. 1976. Overview of analytical identification and spectroscopic properties. In: National Conference on Polychlorinated Biphenyls, Chicago, 1975. EPA-560/6-75-004. Washington, DC: Environmental Protection Agency; p. 94-102. (Cited in IARC 1978)

Safe S. 1980. Halogenated biphenyls, terphenyls, napthalenes, dibenzodioxins and related products. Metabolism uptake, storage and bioaccumulation. Toxicol Environ Health; 4:81-107.

Safe S, Hutzinger O, Jones D. 1975. The mechanism of chlorobiphenyl metabolism. J Agric Food Chem; 23:851-853.

Safe S, Bandiera S, Sawyer T, et al. 1985. PCBs: structure-function relationships and mechanism of action. Environ Health Perspect; 60:47-56.

Safe S, Safe L, Mullin M. 1985. Polychlorinated biphenyls: congener-specific analysis of a commercial mixture and a human milk extract. J Agric Food Chem; 33:24-29.

Sager DB. 1983. Effect of postnatal exposure to polychlorinated biphenyls on adult male reproductive function. Environ Res; 31(1):76-94.

*Sanders OT, Zepp RL, Kirkpatrick RL. 1974. Effect of PCB ingestion on sleeping times, organ weights, food consumption, serum corticosterone and survival of albino mice. Bull Environ Contam Toxicol; 12(4):394-399.

SANSS (Structure and Nomenclature Search System). 1987. Chemical Information System (CIS) computer data base.

Schaeffer E, Greim H, Goessner W. 1984. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol Appl Pharmacol; 75:278-288.

Schecter A, Tiernan T. 1985. Occupational exposure to polychlorinated dioxins, polychlorinated furans, polychlorinated biphenyls, and biphenylenes after an electrical panel and transformer accident in an office building in Binghamton, NY. Environ Health Perspect; 60:305-13.

Schmitt CJ, Zajicek JL, Ribick MA. 1985. National pesticide monitoring program. Residues of organochlorine chemicals in freshwater fish, 1980-1981. Arch Environ Contam Toxicol; 14:225-60.

Schneider JF, Bourne S, Boparai S. 1984. Parallel capillary column gas chromatography in the determination of chlorinated pesticides and PCBs. J Chromatogr; 22(5):203-206.

Schnellmann RG, Putnam CW, Sipes IG. 1983. Metabolism of 2,2',3,3',6,6'-hexachlorobiphenyl and 2,2',4,4',5,5'-hexachlorobiphenyl by human hepatic microsomes. Biochem Pharmacol; 32:3233-3239. (Cited in EPA 1987a)

Schnellmann RG, Volp RF, Putnam CW, Sipes IG. 1984. The hydroxylation, dechlorination and glucuronidation of 4,4'-dichlorobiphenyl by human hepatic microsomes. Biochem Pharmacol; 33:3503-3509. (Cited in EPA 1987a)

Schoeny R. 1982. Mutagenicity testing of chlorinated biphenyls and chlorinated dibenzofurans. Mutat Res; 101:45-56. (Cited in EPA 1987a)

Schoeny RS, Smith CC, Loper JC. 1979. Non-mutagenicity for *Salmonella* of the chlorinated hydrocarbons Aroclor 1254, 1,2,4-trichlorobenzene, mirex and kepone. Mutat Res; 68:125.

Schwartz PM, Jacobson SW, Fein G, Jacobson JL, Price HA. 1983. Lake Michigan fish consumption as a source of polychlorinated biphenyls in human cord serum, maternal serum and milk. Pub Amer J Public Health; 73(3):293-296.

Sipes IG, McLain GE, Jr, Podolsky TL, Brown BR, Jr. 1978. Bioactivation of halothane: Correlation with hepatotoxicity. Int Congr Serx-Excerpta Med; 440:238. (Cited in EPA 1985a)

Sklarew DS, Girvin DC. 1987. Attenuation of polychlorinated biphenyls in soils. Rev Environ Contam Toxicol; 98:1-41.

Smith AB, Schloemer J, Lowry LK, et al. 1981a. Cross-sectional medical survey of a group of workers occupationally exposed to polychlorinated biphenyls (PCBs) at an electrical equipment manufacturing plant. Cincinnati, OH: NIOSH, Division of Surveillance, Hazard Evaluations and Field Studies, and Lipid Research Center, University of Cincinnati Medical Center. (Cited in Drill et al. 1981)

Smith AB, Schloemer J, Lowry LK, et al. 1981b. Cross-sectional medical survey of two groups of workers occupationally exposed to polychlorinated biphenyls (PCBs) in the maintenance, repair, and overhaul of electrical transformers. Cincinnati, OH: NIOSH, Division of Surveillance, Hazard Evaluations and Field Studies, and Lipid Research Center, University of Cincinnati Medical Center. (Cited in Drill et al. 1981)

Smith AB, Schloemer J, Lowry LK, et al. 1981c. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls (PCBs). Cincinnati, OH: NIOSH, Division of Surveillance, Hazard Evaluations and Field Studies, and Lipid Research Center, University of Cincinnati Medical Center. (Cited in Drill et al. 1981)

Smith AB, Schloemer J, Lowry LK, et al. 1982. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. Br J Ind Med; 39:361-369. (Cited in Wolff 1985, Kreiss 1985)

Smrek AL, Needham LL. 1982. Simplified cleanup procedures for adipose tissue containing polychlorinated biphenyls, DDT, and DDT metabolites. Bull Environ Contam Toxicol; 28:718-722.

Sparling J, Fung D, Safe S. 1980. Bromo- and chlorobiphenyl metabolism: GC/MS identification of urinary metabolites and the effects of structure on their rates of excretion. Biomed Mass Spectrom; 7:13-20. (Cited in EPA 1987a)

Spencer F. 1982. An assessment of the reproductive toxic potential of Aroclor 1254 in female Sprague-Dawley rats. Bull Environ Contam Toxicol; 28(3):290-297.

Steinberg KK, Freni-Titulaer LWJ, Rogers TN, et al. 1986. Effects of polychlorinated biphenyls and lipemia on serum analytes. J Toxicol Environ Health; 19:369-381.

Stone PJ, Ed. 1981. Emergency Handling of Hazardous Materials in Surface Transportation. Washington, DC: Bureau of Explosives, Association of American Railroads; p. 418.

Sundstrom G, Hutzinger D, Safe S. 1976a. The metabolism of chlorobephenyls - A review. Chemosphere; 5:267.

Sundstrom G, Hutzinger D, Safe S. 1976b. The metabolism of 2,2',4,4',5,5'-hexachlorobiphenyl by rabbits, rats and mice. Chemosphere; 4:249. (Cited in EPA 1987a)

Swackhamer DL, Armstrong DE. 1986. Estimation of the atmospheric and nonatmospheric contributions and losses of polychlorinated biphenyls for Lake Michigan on the basis of sediment records of remote lakes. Environ Sci Technol; 20(9):879-883.

Tanabe S, Nakagawa Y, Tatsukawa R. 1981. Absorption efficiency and biological half-life of individual chlorobiphenyls in rats treated chlorobiphenyl products. Agric Biol Chem; 45:717-726. (Cited in EPA 1987a)

Tanabe S, Hidaka H, Tatsukawa R. 1983. PCBs and Chlorinated hydrocarbon pesticides in Antarctic atmosphere and hydrosphere. Chemosphere; 12:277-88.

MONS 027390

Tanabe S, Tanaka H, Tatsukawa R. 1984. Polychlorobiphenyls, DDTs and hexachlorocyclohexane isomers in the western North Pacific ecosystem. Arch Environ Contam Toxicol; 13:731-8.

Tatematsu M, Nakanishi K, Murasaki G, Miyata Y, Hirose M, Ito N. 1979. Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by *N*-2-fluorenylacetamide in rats. JNCI; 63(6):1411-1416. (Cited in EPA 1985a)

Taylor PR, Lawrence CE, Hwang HL, Paulson AS. 1984. Polychlorinated biphenyls: Influence on birthweight and gestation. Am J Public Health; 74(10):1153-1154.

*Thomas PT, Hinsdill RD. 1978. Effect of polychlorinated biphenyls on the immune responses of rhesus monkeys and mice. Toxicol Appl Pharmacol; 44:41-51.

Thomas RL, Frank R. 1981. PCBs in sediment and fluvial suspended soilds if the Great Lakes. In: Mackay D, et al., eds. Phys Behav PCDs Great Lakes. Ann Arbor, MI: Ann Arbor Sci; p. 245-67.

Tiernan TO, Taylor ML, Garret JH, et al. 1983. PCDDs, PCDFs and related compounds in the effluents from combustion processes. Chemosphere; 12:595-606.

Tiernan TO, Taylor ML, Garret JH, et al. 1985. Sources and fate of polychlorinated dibenzodioxins, dibenzofurans and related compounds in human environments. Environ Health Perspect; 59:145-58.

*Treon JF, Cleveland FP, Cappel JW, Atchley RW. 1956. The toxicity of the vapours of Aroclor 1242 and Aroclor 1254. Am Ind Hyg Assoc Quart; 17:204-213.

Urabe H, Koda H, Asahi M. 1979. Present data of Yusho patients. Ann NY Acad Sci; 320:273. (Cited in EPA 1985a)

USITC (U.S. International Trade Commission). 1978. Imports of benzenoid chemicals and products 1977. USITC Publication 900. Washington, DC: USITC; p. 26.

USITC (U.S. International Trade Commission). 1979. Imports of benzenoid chemicals and products 1978. USITC Publication 990. Washington, DC: USITC; p. 26.

USITC (U.S. International Trade Commission). 1980. Imports of benzenoid chemicals and products 1979. USITC Publication 1083. Washington, DC: USITC; p. 28.

USITC (U.S. International Trade Commission). 1982. Imports of benzenoid chemicals and products 1981. USITC Publication 1272. Washington, DC: USITC; p. 25.

Vernon AA, et al.** 1981. High levels of polychlorinated biphenyls in serum specimens, Kansas. Internal Report ELI-80-23-2, Centers for Disease Control, Atlanta, November 16, 1981. (Cited in Kreiss 1985)

*Villeneuve DC, Grant DL, Khera K, Clegg DJ, Baer H, Phillips WEJ. 1971. The fetotoxicity of a polychlorinated biphenyl mixture (Aroclor 1254) in the rabbit and in the rat. Environ Physiol; 1:67-71.

Villeneuve DC, Grant DL, Phillips WEJ. 1972. Modification of pentobarbital sleeping times in rats following chronic PCB ingestion. Bull Environ Contam Toxicol; 7:264. (Cited in EPA 1985a)

*Vos JG, Beems RB. 1971. Dermal toxicity studies of technical polychlorinated biphenyls and fractions thereof in rabbits. Toxicol Appl Pharmacol; 19:317-633.

Vos JG, Notenboom-Ram E. 1972. Comparative toxicity study of 2,4,5, 2',4',5'-hexachlorobiphenyl and a polychlorinated biphenyl mixture in rabbits. Toxicol Appl Pharmacol; 23:563-578.

Vos JG, deRoij T. 1972. Immunosuppressive activity of a polychlorinated biphenyl preparation on the humoral immune response in guinea pigs. Toxicol Appl Pharmacol; 21:549-555.

Vos JG, van Genderen H. 1973. Toxicological aspects of immunosuppression. In: Deichman WB, ed. Pesticides in the environment, a continuing controversy. Miami, FL: 8th Int Conf Toxicol Occup Med. New York: Intercontinental Medical Book Co. (Cited in EPA 1987a)

Ward JM. 1985. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Arclor 1254. Environ Health Perspect; 60:89-95.

Watanabe M, Sugahara T. 1981. Experimental formation of cleft palate in mice with polychlorinated biphenyls (PCB). Toxicology; 19(1):49-53. (Cited in EPA 1987a)

Weant GE, McCormick GS. 1984. Nonindustrial sources of potential toxic substances and their applicability to source apportionment methods. EPA 450/4-84-003; NTIS PB84-231232. Research Triangle Park, NC: EPA; p. 36, 86.

Welsch F. 1985. Effects of acute or chronic polychlorinated biphenyl ingestion on maternal metabolic homeostasis and on the manifestations of embryotoxicity caused by cyclophosphamide in mice. Arch Toxicol; 27(2):104-113.

Welty ER. 1983. Personal communication, August 8, 1983. (Cited in Kreiss 1985)

Wickizer TM, Brilliant LB, Copeland R, Tilden R. 1981. Polychlorinated biphenyl contamination of nursing mothers' milk in Michigan. Amer J Pub Health; 71(2):132-137.

Wolff MS. 1983. Occupational derived chemicals in breast milk. Am J Ind Med; 4:259-281. (Cited in EPA 1985a)

Wolff MS. 1985. Occupational exposure to polychlorinated biphenyls (PCBs). Environ Health Perspect; 60:133-8.

Wolff MS, Fischbein A, Thornton J, Rice C, Lillis R, Selikoff IJ. 1982a. Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. Int Arch Occup Environ Health; 49:199-208. (Cited in Kreiss, 1985)

Wolff MS, Thornton J, Fischbein A, Lillis R, Selikoff IJ. 1982b. Disposition of polychlorinated biphenyl congeners in occupationally exposed person. Toxicol Appl Pharmacol; 62(2):294-306.

Wyndham C, Devenish J, Safe S. 1976. The in vitro metabolism, macromolecular binding and bacterial mutagenicity of 4-chlorobiphenyl, a model PCB substrate. Res Commun Chem Pathol Pharmacol; 15:563. (Cited in EPA, 1985a)

Wyss PA, Muhlebach S, Bickel MH. 1986. Long-term pharmacokinetics of 2,2',4,4',5,5'-hexachlorobiphenyl (6-CB) in rats with constant adipose tissue mass. Drug Metab Dispos; 14:361-365. (Cited in EPA 1987a)

Yakushiji T, Watanabe I, Kuwabara et al. 1978. Long-term studies of the excretion of polychlorinated biphenyls (PCBs) through the mother's milk of an occupationally-exposed worker. Arch Environ Toxicol; 7:493-504. (Cited in EPA 1987a)

Yoshimura H, Yamamoto HA. 1975. A novel route of excretion of 2,4,3',4'-tetrachlorobiphenyl in rats. Bull Environ Contam Toxicol; 13:681-388. (Cited in EPA 1985a)

Yoshimura H, Yoshihara S. 1976. Toxicological aspects. II. The metabolic fate of PCBs and their toxicological evaluation. In: Higuchi K, ed. PCB Poisoning and Pollution. Tokyo: Kondansha Ltd; p. 41-67. (Cited in EPA 1985a)

11. GLOSSARY

Acute Exposure--Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Bioconcentration Factor (BCF)--The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure--Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity--The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity--Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

EPA Health Advisory--An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)--The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

MONS 027394

Intermediate Exposure--Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity--The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro--Isolated from the living organism and artificially maintained, as in a test tube.

In vivo--Occurring within the living organism.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

Lethal Concentration(LO) (LC_{LO})--The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})--A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(LO) (LD_{LO})--The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

Malformations--Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level--An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen--A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity--The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

Permissible Exposure Limit (PEL)--An allowable exposure level in workplace air averaged over an 8-h shift.

q_1^*--The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity--The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)--The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

MONS 027396

Target Organ Toxicity--This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen--A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)--A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA)--An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UF)--A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

MONS 027397

APPENDIXES

APPENDIX A: PEER REVIEW

A peer review panel was assembled for PCBs. The panel consisted of the following members: Dr. Rolf Hartung, Chairman, Toxicology Program, University of Michigan; Dr. James Olson, Associate Professor of Pharmacology and Therapeutics, SUNY Buffalo; Dr. Shane Que Hee, Associate Professor of Environmental Health, University of Cincinnati Medical Center. These experts collectively have knowledge of PCB's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated into the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in this record.

MONS 027399

APPENDIX B: *FEDERAL REGISTER* ANNOUNCEMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
ENVIRONMENTAL PROTECTION AGENCY
(ATSDR-2; FRL-3269-7)

NOTICE OF AVAILABILITY OF TOXICOLOGICAL PROFILES

AGENCIES: Department of Health and Human Services (DHHS): Agency for Toxic Substances and Disease Registry (ATSDR); and Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Superfund Amendments and Reauthorization Act (SARA) (Public Law 99-499) amends the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund) (42 U.S.C. 9601 et seq.) by establishing certain requirements for the Agency for Toxic Substances and Disease Registry (ATSDR) of DHHS and EPA with regard to hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List (NPL). Among these statutory requirements is a mandate for the Administrator of ATSDR to prepare toxicological profiles for each substance previously included on the first priority list of 100 chemicals. The list identified the first 100 chemicals which both Agencies determined posed the most significant potential threat to human health. This list was published in the Federal Register on April 17th, 1987 (52 FR 12866) as required by SARA section 110.

This notice announces the expected availability dates of the first 25 draft toxicological profiles for review and comment.

AVAILABILITY: The following draft toxicological profiles are expected to be publicly available by the date indicated:

Date/Profile	CAS #
October 17, 1987:	
Benzo(a)anthracene	56-55-3
Benzo(a)pyrene	50-32-8
Beryllium	7440-41-7
Chloroform	67-66-3
Chromium	7440-47-3
Chrysene	218-01-9
Dibenzo(a,h)anthracene	53-70-3
Heptachlor/Heptachlor epoxide	76-44-8 / 1024-57-3
Nickel	7440-02-0
N-Nitrosodiphenylamine	86-30-6
October 29, 1987:	
Aldrin/dieldrin	309-00-2 / 60-57-1
Arsenic	7440-38-2
Benzo(b)fluoranthene	205-99-2
PCBs - Aroclor 1260, 1254, 1248, 1242, 1232, 1221, 1016	11096-82-5, 11097-69-1, 12672-29-6 53469-21-9, 11141-16-5, 11104-28-2 12674-11-2
2,3,7,8- Tetrachlorodibenzo-p-dioxin	1746-01-6
November 5, 1987	
Benzene	71-43-2
Bis(2-ethylhexyl)phthalate	117-81-7
Cadmium	7440-43-9
1,4-Dichlorobenzene	106-46-7
Methylene chloride	75-09-2
November 30, 1987	
Cyanide	57-12-5
Lead	7439-92-1
Tetrachloroethylene	127-18-4
Trichloroethylene	79-01-6
Vinyl chloride	75-01-4

A full 90-day public comment period will be provided for each profile, starting from the actual release date. The close of the comment period for each draft profile will be indicated on the front of each profile.

Requests for draft toxicological profiles should be sent to:

Ms. Georgi Jones
Director, Office of External Affairs
Agency for Toxic Substances and Disease Registry
Chamblee 28 South
1600 Clifton Rd.
Atlanta, GA 30333

Specify the profiles you wish to review. One copy of each profile requested will be forwarded, free of charge, as they become available. In the case of undue delays, requestors will be notified.

Five copies of all comments should be sent to Ms. Jones at the above address by the end of the comment period. All written comments and the draft profiles will be available for public inspection at the Agency for Toxic Substances and Disease Registry (ATSDR), Building 28 South, Room 1103, 4770 Buford Highway, NE, Chamblee, GA, from 8am to 4:30pm, Monday through Friday, except legal holidays. Written comments and other data submitted in response to this notice and the draft toxicological profiles should bear the docket control number ATSDR-2.

SUPPLEMENTARY INFORMATION:

I. BACKGROUND

On October 17, 1986, the President signed the Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499), which extends and amends the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund, 42 U.S.C. 9601 et seq.).

Section 110 of SARA amends section 104(i) of CERCLA by establishing requirements for the preparation of: (1) lists of hazardous substances in order of priority, (2) toxicological profiles of those substances, and (3) a research program to fill data gaps associated with the substances.

In compliance with section 104(i)(2)(A) of CERCLA, ATSDR and EPA published on April 17, 1987 (52 FR 12866) the first priority list of 100 hazardous substances. This priority list of 100 was further broken down into four groups of 25 chemicals. The first group of 25 was to be the subject of the second phase of the requirements, i.e., the development of the first set of toxicological profiles. Section 104(i)(3) of CERCLA spells out the content of these profiles and the timetable by which they must be developed. Profiles on at least 25 substances on the first priority list were to be completed within one year of the enactment of SARA (by October 17, 1987). The remaining seventy-five are to be completed at a rate of at least twenty-five per year with the total 100 completed within four years after the enactment of the SARA amendments. Revision and republication is mandated as necessary but no less often than once every three years.

Each profile is required to include an examination, summary and interpretation of available toxicological information and epidemiologic evaluations. This information and data are to be used to ascertain the levels of significant human exposure for the substance and the associated health effects. The profiles must also include a determination of whether adequate information on the health effects of each substance is available or in the process of development. The Agencies' intention is that this information be used to identify the key toxicological testing needs that when filled will improve our ability to define significant human exposure levels.

The toxicological profiles are to be provided to the States and made available to the public. The profiles are to be prepared in accordance with the guidelines developed by ATSDR and EPA. These guidelines were published along with the priority list of 100 in the April 17, 1987 Federal Register Notice (52 FR 12870).

This current notice announces the projected availability dates of the first 25 draft toxicological profiles. The documents have undergone extensive internal review and have been subject to scientific and technical peer review by outside experts. We are now announcing their availability and encouraging public participation and comment on the further development of these profiles. Although the profiles will not be completed by the October 17, 1987 deadline, we believe that the extra time given to peer review and public review and comment is important to the development of quality profiles of scientific merit.

Although we are reasonably confident that the key studies for each of the 25 substances were considered during the profile development process, this *Federal Register* notice solicits any significant studies, including unpublished data, which may aid the revision of these draft profiles.

II. LEVELS OF SIGNIFICANT HUMAN EXPOSURE

The setting of specific levels of significant human exposure has presented a unique set of problems. The significance of a specific level of a hazardous substance depends on the context in which that level is evaluated. For example, a low level that may be insignificant with respect to causing acute, immediately debilitating symptoms may be highly significant with respect to causing gradual, chronic effects over a longer term. Since these profiles are intended for use by a diverse group of people who have different situations in which to interpret the significance of specific levels, it was considered appropriate at this time to describe the range of exposures over which effects may occur (where data are available), and to allow the user to make determinations as to which type of effect is significant in any particular instance. A format for graphically displaying the levels of significant human exposure has been developed and is used in the profiles to present the ranges over which effects may be observed.

We encourage public comment and recommendations on this specific issue.

III. SOLICITATION OF PUBLIC COMMENT

We are soliciting public comment on all phases of the development of the toxicological profiles. A previous Federal Register notice, published on April 17, 1987 (52 FR 12866) solicited comment on the first priority list of hazardous substances. We are currently reviewing those comments and are evaluating the impact that those comments may have on the priority list and the methods used in its development.

As the first 25 toxicological profiles become available in draft form, we are eager to provide them to the States, industry, public health professionals, scientists and the general public. We welcome comment and feedback on the content of the profiles; the format and scope of the documents; the process used in the development of the levels of significant human exposure and the overall process used in the development of the profiles.

There are specific items that we would like to draw to the attention of the reader and would strongly encourage as candidates for close attention during the comment period.

A. PUBLIC HEALTH STATEMENT

The draft profiles include a public health statement which is intended to provide the lay public with a concise statement of the general health risks associated with the chemical of concern. The summary as originally planned should be able to stand alone. If removed from the rest of the document, it should still be capable of conveying

to the public the substantive health concerns associated with the substance. We are also considering the development of more abbreviated versions of the public health statements and are evaluating a number of different formats. This notice specifically invites comments on the existing public health effects statements in the draft profiles and solicits recommendations for alternative approaches.

B. DATA/STUDIES USED IN THE DEVELOPMENT OF THE PROFILES

In general, and for each chemical-specific profile, have the appropriate studies been used in the development of these documents? Our concern here is that we capture the critical, or "key", studies but not miss other data that may be important in the valid evaluation of the toxicological profile chemicals.

C. FORMAT AND CONTENT OF THE PROFILES

The draft profiles represent our best effort to provide the information required by Section 104 (i)(3) of CERCLA in the most useful format for the various identified users of the profiles, given the constraints of the tight timeframe. Every effort has been made to define sections clearly and to format the documents in such a way that they can be used as resource documents by many different audiences. We specifically request comment on the format and content of the initial set of profiles, including how the format might be modified for subsequent sets of profiles.

D. LEVELS OF SIGNIFICANT HUMAN EXPOSURE

What is the most useful way of presenting this type of information? For this first generation of profiles we have selected a graphic presentation that reflects a "range" of values that covers both upper and lower bounds of effect levels. Is this more useful than a single number? Are there other ways of presenting this type of information that would be more useful to the eventual user?

E. IDENTIFICATION OF SIGNIFICANT DATA GAPS

The process used to develop the draft profiles has resulted in the identification of the full range of health effects data gaps associated with each chemical. However, depending on individual circumstances some subset of the identified data gaps may be essential in determining levels of significant exposure, while other data gaps may be less immediate. ATSDR, EPA, and the National Toxicology Program (NTP) have been exploring ways to identify the critical data elements that are needed to establish significant human exposure levels. This notice specifically requests comment and suggestions for approaching this phase of the toxicological profile process.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Agency for Toxic Substances and Disease Registry
Atlanta GA 30333

Official Business
Penalty for Private Use $300

SPECIAL
FOURTH-CLASS RATE
POSTAGE & FEES PAID
PHS/CDC
Permit No. G 284

DENISE RECTOR
MONSANTO COMPANY
800 N LINDBERGH BOULEVARD
ST LOUIS MO 63167

MONS 027406

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO. SAB-EHC-88-019	2.	3. PB89-105045

4. Title and Subtitle: Review of the Draft Drinking Water Criteria Document for Polychlorinated Biphenyls PCBs	5. Report Date: Mar. 9, 1988
	6.
7. Author(s): Environmental Health Committee	8. Performing Organization Rept. No.
9. Performing Organization Name and Address: Environmental Protection Agency, Science Advisory Board, 499 S. Capitol Street, SW, Washington, D.C. 20460 (A101F)	10. Project/Task/Work Unit No.
	11. Contract(C) or Grant(G) No. (C) (G)
12. Sponsoring Organization Name and Address: Environmental Protection Agency, 401 M Street, SW, Washington, D.C. 20460 (A101)	13. Type of Report & Period Covered: Final Report
	14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

The Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee completed its independent scientific review of the Draft Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs). The review was conducted in Washington, D.C. November 19-20, 1987.
The major recommendation of the Subcommittee was that the U. S. Environmental Protection Agency explore whether the available data on PCB congeners can be developed on a scale of toxicity similar to the toxicity equivalency factor that the Agency had already prepared for dioxins. This efforts could potentially yield some scientifically interesting insights relating to uncertainties in the PCB data base even if it represents only an approximation in which data analysis and scientific judgment are combined. In general the Subcommittee concluded that the document suffers from a failure to clearly identify its scientific objectives.

17. Document Analysis a. Descriptors

Environmental Health Committee

b. Identifiers/Open-Ended Terms

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
	20. Security Class (This Page)	22. Price

(See ANSI-Z39.18) See Instructions on Reverse OPTIONAL FORM 272 (4-77) Formerly NTIS-35) Department of Commerce

MONS 027407

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

March 9, 1988

Hon. Lee M. Thomas
Administrator
U.S. Environmental Protection
Agency
401 M Street, SW
Washington, D.C. 20460

SAB-EHC-88-019

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee has completed its independent scientific review of the Draft Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs) and is pleased to transmit its final report to you. The Subcommittee conducted a public review of the draft criteria document at a meeting held in Washington, D.C. on November 19-20, 1987.

In general, the Subcommittee concludes that the document suffers from a failure to clearly identify its scientific objectives. Subcommittee members encountered a myriad of facts that were not critically presented in order to support subsequent regulatory decisions. For example, the document must state a scientific rationale to enable risk managers to decide whether to regulate Aroclors or PCBs in the environment. While sections of the document are improved from a previous draft, other chapters, discussed in the attached report, require extensive revision before the document as a whole represents a scientifically adequate statement of existing knowledge for PCBs.

A major recommendation of the Subcommittee is that EPA explore whether the available data on PCB congeners can be developed on a scale of toxicity, similar to the toxicity equivalency factor that EPA has already prepared for dioxins. This effort could potentially yield some scientifically interesting insights relating to uncertainties in the PCB data base, even if it represents only an approximation in which data analysis and scientific judgment are combined.

The Subcommittee appreciates the opportunity to conduct this particular scientific review. We request that the Agency formally respond to the scientific advice presented in the attached report.

Sincerely,

Norton Nelson, Chairman
Executive Committee

Richard A. Griesemer, Chairman
Environmental Health Committee

John Doull, Chairman
Halogenated Organics Subcommittee

MONS 027408

II. Specific Technical Comments and Recommendations

1. Concerning the contributions from contaminant toxicity, the document needs to more critically address the claims that PCDFs were absent from some Aroclor preparations. In describing a number of studies, it is indicated that the PCBs (individual congeners or mixtures) are free of dibenzofurans. Examples of such statements have already been transmitted to EPA. In many instances, it is stated that there was only "apparently" no dibenzofuran contamination, and in no instance was the claim carefully and critically documented. The draft criteria document probably provides sufficient and adequate information to partially resolve the issue of dibenzofuran contribution to observed Aroclor toxicity. Comparisons of studies using PCB mixtures, with and without dibenzofuran contamination, and comparisons of studies with purified individual PCB congeners and with mixtures should be made in the draft document. Studies such as the one recently published that indicates that the toxicity of dioxins can be diminished by co-administered Aroclors should be taken into account in assessing a role for PCDFs in PCB mixture toxicity.[2]

2. The conclusion (page III-26, line 10 and page III-42, paragraph 2, line 5) that the rat is a good model for human metabolism of PCBs is based upon a gross oversimplification since only three distinct congeners were evaluated, and the correlation is more relative than absolute. The statements should be modified or deleted.

3. The draft document is somewhat ambiguous concerning a role of metabolism in PCB toxicity. On the one hand, the less highly chlorinated congeners, and particularly those with unchlorinated vicinal carbons, are the most highly metabolized (page III-37, points 3 and 4, and pages V-53 and 55). This metabolism is erroneously associated with aspects of toxicity (page III-40, paragraph 2 and page VII-11). On the other hand, the more highly chlorinated congeners which are minimally metabolized are reported to be the most toxic.

Metabolism plays a role in PCB toxicity, and cytochromes P-450 are involved. Furthermore, PCBs can differentially induce cytochromes P-450 and thus affect their own metabolism and toxicity during chronic and subchronic exposures—a fact not discussed in the criteria document. For example, PCB exposure from food could induce hepatic cytochromes P-450, which would affect the fate of the more readily metabolized PCB congeners. The role of different forms of cytochrome P-450 in PCB metabolism should be discussed.[3]

4. Analytical measurement of PCBs in water provides no indication of an equivalent Aroclor concentration, and application of Aroclor toxicities to such equivalent contamination is without any reasonable scientific basis and cannot be used as the basis for regulatory decision making. Specific congener analysis is more precise, accurate and well-suited to PCBs exposed to physical, chemical or biotic forces. Unfortunately, not all specific congener analyses

are equal, and they are frequently not comparable. The most thorough analysis (Safe et. al., 1985) is too ambitious at this time for routine monitoring and cannot be applied retroactively to the vast data bank needed to determine trends. The inequalities of specific congener analyses can be very misleading, if not recognized. For example, Ballschmiter and Zell do not consider PCBs 84, 110, 141 and 149 in their 1980 paper. Likewise, Schwartz et. al., (1987) omit these congeners even though Sissons and Welti (1971), Webb and McCall (1972), Bush et. al., (1983) and Safe et. al., (1985) have confirmed their significant presence. In addition, PCB 95 is reported at low levels by some authors and higher levels are observed in the same PCB by others. Therefore, the problem extends beyond specific congener analysis verses Aroclor estimates. Ambiguities and disagreements should be cited to a limited extent in any precautionary statement, perhaps as a repeating footnote.

The task of resolving conflicting reports and selective congener identifications is monumental. Certainly the current document cannot resolve this issue. Nevertheless, it appears to be a disservice to state that, "10 of the 19 congeners were unambiguously from Aroclor 1016" (page IV-3). Several of these monochloro- to tetrachloro-congeners are also found in Aroclors 1232, 1242 and 1248 (Webb and McCall, 1972) as well as low levels in 1260 (Safe). This is further confirmed on page IV-6 in Table IV-1.

Also, on pages IV-8 and 9 the congener composition that is "compatible" with 24, 42 and 34% Aroclors 1242, 1254 and 1260 requires some qualification since lower chlorinated congeners might dissolve out and/or be degraded, and the sediment would be enriched in higher chlorinated congeners because of solubility and binding to particulates. Later in the same paragraph, it was stated that Lake Superior water contained 37-56% of Aroclor 1242, while years later the sediments contained 15-21%. Also, Table IV-2 shows higher 1242 in the aqueous phase compared to particulate precipitation, while 1254 and 1260 are about equal in rain and much higher in snow particulates than in the aqueous phase.

Thus, it is known that chlorobiphenyls partition in these ways, and this affects residue composition. The apparent Aroclor composition can and does seem to change. Cautioning that these things happen and that scientists must recognize that Aroclor estimates may be misleading, and subsequently trying to force a mixed residue to fit the pattern(s) of specific Aroclor(s) is inconsistent and must be rectified in the document. For example, page V-95, Table V-21 indicates grossly different compositions of Aroclor 1260 which are most likely a consequence of analytical methodology differences.

Knowing that specific congener analyses are not equal also does little good if there are not attempts to resolve the inequalities. By throwing out PCB data with some ambiguities, there would be virtually no data to assess. Moreover, the vast amount of data available would yield even more information if attempts to force a convenient fit would be avoided. The ambiguities and forced fits do not invalidate the data that are vital to the types of considerations that need to be undertaken.

In summary, the Subcommittee recommends that a simple two-footnote qualification system be developed stating that: 1) when Aroclor estimates are used, there should be references to an appendix page stressing the problems, inferences and possible valuable information: and 2) when specific congener analyses are used, subsequent pages should present some of the ambiguities and appropriate precautions.

5. There is evidence for PCB metabolite binding to protein, DNA and RNA (page III-40) and DNA damage by metabolites (page III-41). However, the mutagenicity data presented in the document show that the PCBs tested do not induce gene mutations in either prokaryote or eukaryote test systems. Similar studies testing the ability of PCBs to induce clastogenic effects, i.e. chromosome aberrations resulting from chromosome breakage and re-arrangements, were also negative. Thus, the conclusion, to date, would be that the PCBs studied provide no evidence for genotoxicity, namely no induced DNA damage.

On the other hand, there is a possibly conflicting result in the studies with Drosophila. Here, exposure to purified Clophen-A-50 (at certain doses) has resulted in significant increases in exceptional XO flies. This means that either X or Y chromosomes were lost in development of the male germ line. Such chromosome loss could result either from chromosome breakage or non-disjuction. Non-disjunction may be induced by damaging the spindle fibers (tubulin protein), the centrosomes and/or other elements of the mitotic apparatus such that the chromosomes are improperly segregated in meiosis. Thus, a mutagenic, but not genotoxic, endpoint is possibly induced by some PCBs leading to cellular aneuploidy (unbalanced chromosome numbers). The Subcommittee recommends that this phenomenon be discussed because it may provide additional insight into the mechanism of carcinogenesis.

6. In reaching a regulatory decision for PCBs in drinking water, the Subcommittee recommends that a modified version of Option I (see attached issue paper provided by the Office of Drinking Water) be adopted. It is not necessary to derive criteria for drinking water for each PCB isomer/congener but, rather, only for the more toxic ones. A scale of toxicities for PCB isomers/congeners should be prepared and an "equivalency approach" developed, using the most toxic PCBs as the basis for comparison. All available data on PCB congener toxicity should be used in deriving a toxicity scale, including cytochrome P-450 and non-Ah receptor effects and induction data. Although the Subcommittee recognizes that some of these data cannot be considered "toxicologic," it concludes that this will not negate derivation of a reasonable approximation. A similar approach is currently used by EPA and other governmental agencies for halogenated dibensofurans and dibenzodioxins. Once such a scale of toxicities is developed it can be used as a guide in selecting congeners of major significance for regulatory decisions. This approach will have the advantage over Option III in that any PCB mixture can be analyzed and decisions made and defended.

References

1. Bondiera, et. al., Chemosphere 13 (1984), 507: and Kunita, et. al., American Journal of Ind. Med., 5 (1984), 45.

2. Bulletin of Environmental Contam. Toxicol., 39 (1987), 791.

3. Biochem. Pharmacol., 30 (1981), 577-588, and 29 (1980), 729-736; and Biochemistry 20 (1984), 7379-7384.

Note to the Reader

Dr. Stephen Safe, a consultant to the Halogenated Organics Subcommittee, did not formally vote to approve this Subcommittee report because of a prior involvment in the preparation of the draft criteria document. He did participate in the public meeting in which the Subcommittee reviewed the draft document but served in the capacity as a resource to clarify specific technical issues.

MONS 027412

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
Roster for November 19-20, 1987 Review of the Draft Final
Drinking Water Criteria Document for Polychlorinated Biphenyls

Dr. John Doull, Chairman, Professor of Pharmacology and Toxicology, University of Kansas Medical Center, Kansas City, Kansas 66103 (913) 588-7508 or

Dr. Seymour Abrahamson, Vice-Chairman, Professor of Zoology and Genetics, Department of Zoology, University of Wisconsin, Madison, Wisconsin 53706

Subcommittee Members and Consultants

Dr. George T. Bryan, Department of Human Oncology, K-4, Room 528, 608 Clinical Science Center, 600 Highland Ave., University of Wisconsin, Madison, Wisconsin 53792

Dr. Larry Hansen, College of Veterinary Medicine, University of Illinois, 2001 South Lincoln, Urbana, Illinois 61801

Dr. Ronald D. Hood, Professor and Coordinator, Cell and Developmental Biology Section, Department of Biology, University of Alabama, and Principal Associate, R. D. Hood and Associates, Consulting Toxicologists, P. O. Box 1927, University, Alabama 35486

Dr. Larry Kaminsky, Director Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, New York 12201

Dr. Curtis Klaassen, Professor of Pharmacology and Toxicology, University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Kansas 66103

Dr. Don E. McMillan, Chairman, Department of Pharmacology, Mail #638, University of Arkansas, Medical Sciences, 4301 West Markham, St. Little Rock, Arkansas 72205

Dr. Martha Radike, University of Cincinnati Medical Center, Department of Environmental Health 3223 Eden Avenue—M. L. #56, Cincinnati, Ohio 45267

Dr. Thomas Starr, CIIT, P. O. Box 12137, Research Triangle Park, North Carolina 27709

Executive Secretary

Dr. C. Richard Cothern, Executive Secretary, Environmental Health Committee, Science Advisory Board (A-101F), U.S. Environmental Protection Agency 401 M Street, SW, Washington, D.C. 20460

MONS 027413

I. Background:

Appreciable levels of PCBs were detected in ground water samples from wells near highly industrialized and landfill areas of New Jersey. Surface water, sediments and fish from a good number of rivers in the U.S. and in the Great Lakes were found to contain PCBs. PCBs were also detected in tap water samples of a few communities which obtain their water from the highly contaminated Hudson River. However, none of the above ground water and municipal tap water surveys identified the specific Arochlor mixture in drinking water samples. There is only one published report which identified Aroclor 1016 mixture, at levels as high as 100 ng/l, in samples from a small upstate New York public water supply system. The two reservoirs of this waterworks, where Aroclor 1016 was also detected, used the Hudson River as their source of water. Higher chlorinated Aroclor mixtures were present in the Hudson River and in one of the reservoirs but not detected in the finished drinking water samples from this community.

Polychlorinated biphenyls pose special problems with respect to establishing meaningful drinking water regulations. There are 209 different PCB isomers and it seems only 100 individual isomers have been identified at significant levels in commercial mixtures. Although toxicological studies have been performed on only a small number of the Aroclor mixtures, it is evident that there are significant differences in toxicity between different isomers and congeners. In particular, toxicity appears to increase with increasing chlorine content, and isomers which are axially substituted (positions 3,4,and 5) are more toxic than species that are substituted in positions 2 and 6. Consequently, the toxicity of PCB mixtures depends on the isomer-specific composition of the mixture, as illustrated by the differing chronic toxicities of various commercial PCB formulations. In addition, different PCB preparations may differ considerably in the content of toxic contaminants, such as polychlorinated dibenzofurans.

For these reasons, toxicity data derived from a particular commercial PCB formulation are not directly applicable to other formulations, and may not even be applicable to different batches of the same formulation. More importantly, toxicity data from studies of commercial PCB formulations may have little relevance to the toxicity of PCBs in drinking water because the composition of environmental mixtures is markedly changed from the parent contaminant as a consequence of differing solubility and stability characteristics of the PCB isomers. Since the toxicity of a mixture could be dominated by a few relatively minor but highly toxic constituent isomers or contaminants, measurement of total concentration is not an adequate index for assessing the toxicity of PCB mixtures.

II. Issue:

Based on the information on the toxicity of PCBs (mixtures, isomers and congeners) and on their solubility and stability in drinking water, is it possible to develop meaningful acceptable concentrations of PCBs in drinking water?

III. Options

Option I

• Consider evaluating the toxicity of individual isomers and derive criteria for drinking water for each isomer, if the data permit. This is a scientifically sound method for addressing the toxicity of PCB mixtures. This approach is not feasible at present, both because isomer-specific toxicity data are not available and because isomer specific analysis of water is not feasible on a routine basis.

Option II

• Assume that all PCB mixtures in the environment are composed entirely of the most highly toxic isomer (3,4,5,3',4',5' hexachlorobiphenyl) and use this to estimate acceptable level of PCBs in drinking water. This will be the most conservative, approach. While this would be certainly protective, this isomer is a minor component of most formulations and has low solubility in water. This option may not be protective of the carcinogenic potential of PCBs because of the lack of data on the carcinogenic potential of this isomer.

Option III

• Assume that a mixture of PCBs in water retains an average toxicity that is not greatly different from that of the parent formulation. Based on this assumption, acceptable levels could be derived for commercial formulations as if they were individual chemicals. One disadvantage to this approach is that it is usually difficult to identify which specific PCBs formulation(s) is (are) the source of PCBs in drinking water.

IV. Recommendation:

Option III is recommended. The key assumption upon which this option rests (that PCBs in water retain an average toxicity similar to the parent formulation) may not be true. However, it is unlikely to underestimate risk since the more toxic higher chlorinated isomers would have least water transport potential. Changes in the acceptable levels of PCBs in drinking water or in the basic regulatory approach may be possible in the future as additional data and techniques become available.

V. Points Of Interest:

1. PCB cancer potency: Comparison with the human evidence (Discussion to be added to document)

The Agency's cancer potency for PCBs (calculated from the Norback and Weltman rat study and reported in the May 1987 Drinking Water Criteria Document to be 7.7 per mg/kg/d continuous lifetime exposure) comperes favorably to the number of cancer cases seen following the rice-oil incident in Japan. Although more cancer cases may be reported in the future, a rough calculation can be made from currently available information.

The Drinking Water Criteria Document (page VI-14, attributed to Kuratsune) reports the average amount of PCBs consumed during the riceoil incident to be about 2 grams. Dividing this by 70 kg (the weight of a typical adult) and by 25,600 days (the number of days in a typical 70-year lifespan), the average daily exposure is estimated to be about 0.0011 mg/kg/d. Multiplying this by 7.7 per mg/kg/d (the Agency's cancer potency) shows the risk to be 847 per 100,000. In an exposed population of 1761 (page VI-31, attributed to Kuratsune) approximately 14.9 excess cancer cases are expected. This projection is not inconsistent with the 7.39 excess liver cancer cases reported to date (page VI-31, 9 observed minus 1.61 expected).

Several major sources of uncertainty in this comparison should be noted: .

a. The Agency's potency estimate is a plausible upper bound, which would tend to overestimate the number of cancer cases.

b. The rice oil was contaminated with polychlorinated dibenzofurans at a level 250 times more concentrated than in the commercial PCB product Kanechlor 500. To the extent that these dibenzofurans are responsible for the observed cancer cases, a projection based on based on the cancer potency of PCBs alone would tend to underestimate the number of cancer cases.

c. Calculating an average daily exposure prorated over an entire lifetime is very problematical, since the exposure was intense but of short duration. In the absence of evidence to the contrary on PCBs, this approach is consistent with the Agency's cancer guidelines. Nevertheless, it remains a substantial source of uncertainty.

Review of the Draft Drinking Water Criteria Document
for Polychlorinated Biphenyls (PCBs)
by the
Halogenated Organics Subcommittee
Environmental Health Committee
Science Advisory Board

I. General Comments

The regulation of PCBs in drinking water or, in fact, any environmental medium, encounters many problems, including several involving the existing scientific data base. All are described in the criteria document, but virtually none are resolved. These scientific problems include the complexity provided by 209 different congeners and isomers present in commercial PCB mixtures, each with a different toxicity; the presence of highly toxic non-PCB components such as polychlorinated dibenzofurans (PCBFs); the differential rates of removal of PCB congeners from the environment which leads to differences in congener profiles from those of the original pollutant mixtures; and the incomplete knowledge of individual PCB congener toxicity.

The draft criteria document suffers from a failure to clearly identify its scientific objectives. Thus, as reviewers, the Subcommittee members encountered a myriad of facts that were not critically applied, either directly or to support a hypothesis for subsequent regulatory decisions. It must be initially resolved whether the objective is to regulate Aroclors or PCBs in the environment. The Subcommittee believes there is a need to more precisely define what is meant by the term "PCBs", in part because Aroclors may or may not be PCB compounds and because of the varied composition of PCB mixtures.

The Subcommittee recommends that the available data on PCB congeners be developed on a scale of congener toxicity, even if this is only an approximation in which data and professional judgment are combined. Any such scale will be Any such scale will be imperfect, however. For example, it is unlikely that the adverse health consequences of thalidomide would be detected.

The draft document has improved considerably from a previous version. There are, however, some sections that require extensive revisions before it represents a scientifically adequate statement of existing knowledge. A major problem with chapters V, VI and VIII is that they are out of date. For example, in chapter V all of the recent structure activity relationships (SAR) for PCBs have been ignored even though they are discussed in detail in chapter VII. The chapter on human health effects almost completely omits a series of papers in Environmental Health Perspectives (volumes 59 and 60) and the American Journal of Ind. Medicine (volume 5) that discuss Yusho/YuCheng poisoning in Japan and Taiwan, and occupational exposures. These omissions severely compromise the quality of this chapter. In addition, it has been shown by two studies that the major etiologic agents in Yusho and YuCheng poisoning are PCDFs.[1] This does not, however, absolve PCBs as toxic agents and as contributors to some of the symptom of Yusho and Yucheng poisining.

MONS 027417

OCCUPATIONAL EXPOSURE TO PCBs AND VARIOUS CANCERS

Report by the
Industrial Disease Standards Panel

IDSP Report No. 2

December, 1987

COMMENTS

by the

NATIONAL ELECTRICAL MANUFACTURERS ASSOCIATION

WASHINGTON, D.C. USA

March, 1988

MONS 027418

National Electrical Manufacturers Association
2101 L Street N.W. Suite 300
Washington D.C. 20037 (202) 457-8400

March 8, 1988

Daniel K. Shipp
Vice President
Public Affairs

Dr. Robert G. Elgie
Chairman
Workers' Compensation Board
2 Bloor Street East, 20th Floor
Toronto, Ontario
Canada M4W 3C3

Dear Dr. Elgie:

The National Electrical Manufacturers Association (NEMA) submits comments in this letter on the Report to the Workers' Compensation Board on Occupational Exposure to PCBs and Various Cancers prepared by the Industrial Disease Standards Panel (IDSP Report No. 2) dated December, 1987. NEMA, which represents manufacturers of electrical equipment such as transformers and capacitors, has had a long and very close involvement with PCBs even pre-dating enactment of the Toxic Substances Control Act (TSCA) in the United States which specifically banned further manufacture of PCBs and is gradually phasing out their continued use.

NEMA also has a close association with the Electrical and Electronic Manufacturers Association of Canada (EEMAC) with several manufacturers having production facilities in both countries.

In making these comments, we have drawn upon our own extensive experience and knowledge of the health effects of PCBs. In addition we have asked Dr. Jack S. Mandel of the University of Minnesota to provide an objective scientific review of the IDSP report. The review of Dr. Mandel and his associates is attached and forms the basis for our comments.

We believe that the large body of toxicologic and epidemiologic data does not justify findings of the Panel that there is a "probable connection between liver, biliary tract and gall bladder cancers and occupational exposure to PCBs." To the contrary, we believe the evidence does not support this finding.

Animal Studies

The review of the animal studies by the Panel is not complete and does not include a balanced perspective on the studies. Studies showing an increase in liver carcinoma did not show an increase in total tumor incidence, in fact, some show a decrease in the non-liver carcinomas. In two of the studies mortality among the PCB exposed animals was actually decreased.

The studies do not "demonstrate reasonable consistency" as stated in the Panel's report. The studies are inconsistent, and part of this inconsistency possibly stems from comparing the carcinogenicity of the different commercial PCB mixtures. Results show an association between fairly large doses of only the most highly chlorinated (e.g. Kanechlor 500 or Aroclor 1260) PCB compounds and site-specific (liver) tumors. The effect appears to be species-specific (primarily in rats).

Extrapolation of the isolated findings in animals to humans is tenuous at best.

Epidemiology Studies

We do not believe the Bradford Hill criteria to assess the causal significance of an association are met. Contrary to claims in the Panel report, association is neither strong nor consistent. The strength of the association is substantially reduced if a two-tailed test is used, if an adjustment is made for multiple hypotheses testing, if only liver cancers are considered and the effect of confounding factors is removed. Consistency is not demonstrated since the individual studies do not all show a significant association. No dose-response relationship has been demonstrated.

None of the individual human mortality studies presented by the Panel shows a significant association. The authors of these reports conclude that no association has been demonstrated. None of these studies accounted for confounding factors such as alcohol use, hepatitis infection, or use of oral contraceptives, known risk factor for liver cancer.

All the studies lumped together cancers of the liver, biliary tract and gall bladder even though the animal studies dealt primarily with liver cancer. Of the seven cancers of the liver, biliary tract or gall bladder considered to be significant, four people had a duration of employment of one year or less, three were not confirmed and only two were classified on the death certificate as primary liver cancer. Three of the seven cancer cases occurred in one plant (Massachusetts) in one study (Brown and Jones). None of these was a primary cancer of the liver. Two of the three cases worked 1.5 years or less.

The use of a meta-analysis to sum the observed and expected results from the "five" studies is questionable because of the substantial dissimilarities among the studies. Such aggregated analyses have been used to date only with randomized controlled trials.

In summary, we do not agree with the finding of the Panel of a "probable connection between liver, biliary tract and gall bladder cancers and occupational exposure to PCBs". Based upon our analysis of the data presented in the IDSP Report, we are convinced that the evidence is not strong and the association cannot be considered causal. "Strong" and "causal" are used to describe associations such as those between cigarette smoking and lung cancer or asbestos and mesothelioma where the data are consistent and persuasive. To use these words to characterize the association between liver cancer and PCB exposure is to distort and grossly exaggerate the weak and inconsistent data that are available.

We appreciate the opportunity to submit these comments to the Workers' Compensation Board of Ontario and trust that they will be given fair consideration. Please feel free to contact either me or Dr. Mandel directly should you need clarification of our remarks. We are also very willing to come to Toronto to discuss our review with the Board.

Very truly yours,

D K Shoff /DGB

DGB/bs

cc: Ms. Linda Angove,
Acting Secretary of the Board

A Review of

"Report to the Workers Compensation Board
on Occupational Exposures to PCBs and
Various Cancers"
IDSP Report No. 2

Submitted by

Jack S. Mandel, Ph.D., M.P.H., Allan Williams, M.A., M.P.H.
and Pat Coin, Ph.D. (cand.)

March 1, 1988

MONS 027422

Summary

Animal Studies

1. The review of the animal studies by the Panel is not complete and does not include a balanced perspective on the studies.

2. The results from the animal studies show an association between fairly large doses of only the most highly chlorinated (e.g. Kanechlor 500 or Aroclor 1260) PCB compounds and site-specific (liver) tumors. The effect appears to be species-specific (primarily in rats).

3. Extrapolation of the isolated findings in animals to humans is tenuous at best.

Human Mortality Studies

4. None of the individual human mortality studies presented by the Panel shows a significant association. The authors of these reports conclude that no association has been demonstrated.

5. None of these studies accounted for confounding factors such as alcohol use, hepatitis infection, or use of oral contraceptives, known risk factors for liver cancer.

6. All the studies lumped together cancers of the liver, biliary tract and gallbladder even though the animal studies dealt primarily with liver cancer.

7. The use of a meta-analysis to sum the observed and expected results from the "five" studies is questionnable because of the substantial dissimilarities among the studies.

MONS 027423

8. The use of a one-tailed statistical significance test is not appropriate.

9. No account was made for the fact that 21 tests were conducted to determine significance. Chance alone would result in the significance of one SMR. An adjustment to the p value should be made for multiple hypotheses testing.

10. Of the 7 cancers of the liver, biliary tract or gallbladder considered to be significant, 4 had a duration of employment of one year or less, 3 were not confirmed and only 2 were classified on the death certificate as primary liver cancer.

11. No dose-response effect was demonstrated.

12. Three of the 7 cancer cases occurred in one plant (Massachusetts) in one study (Brown and Jones). None of these was a primary cancer of the liver. Two of the 3 cases worked 1.5 years or less.

13. The Bradford-Hill criteria to assess the causal significance of an association are not met. The strength of the association is substantially reduced if a two-tailed test is used, if an adjustment is made for multiple hypotheses testing, if only liver cancers are considered and the effect of confounding factors is removed. Consistency is not demonstrated since the individual studies do not all show a significant association. No dose-response relationship has been demonstrated.

MONS 027424

Review of "Report to the Workers Compensation Board on Occupational Exposure to PCBs and Various Cancers" *IOSP Report No. 2*

Introduction

In December 1987, the Industrial Disease Standards Panel of the Ontario Ministry of Labor submitted to the Workers' Compensation Board a report on occupational exposure to polychlorinated biphenyls (PCBs) and cancers. This report was in response to a request from the Workers' Compensation Board to consider the issue of the human carcinogenicity of PCBs for purposes of determining entitlement for workers occupationally exposed to PCBs who have developed cancer. The basis of the Panel's recommendations is the "Report of the Special Panel on Occupational PCB Exposure and Various Cancers: Human Health Effects and Carcinogenic Risk Potential of PCBs". This Special Panel, chaired by Dr. William Nicholson of the Mount Sinai School of Medicine, New York, reviewed the experimental animal studies and observational human studies and conducted a meta-analysis of the epidemiologic mortality studies to reach the conclusion that there is, "a probable connection between liver, biliary tract and gallbladder cancers and occupational exposure to PCBs". Following is a critical review of the Special Panel's report.

Experimental Animal Studies

Although the Special Panel does not explicitly define the scope of, or approach to, the review of the experimental PCB literature, it appears that the Panel sought to provide a somewhat broad and general overview of this literature, as opposed to a comprehensive and critical review. The Panel

MONS 027425

cites most, but not all, of the major animal studies cited by other reviewers. Furthermore, they do not discuss all the important findings in the studies that they review.

The first study cited on PCB-induced liver cancer was that of Ito et al., 1973, who fed male mice a diet of 100, 250, or 500 ppm of Kanechlor 300, Kanechlor 400, or Kanechlor 500. Neoplastic nodules and hepatocellular carcinomas were seen after 32 weeks only in the group exposed to 500 ppm of Kanechlor 500. Seven of 12 animals were found to have neoplastic nodules and 5 of 12 hepatocellular carcinomas. It should be noted that the effect was observed only in the mice fed the diet with the greatest (500 ppm) dose and most chlorinated (54%) PCB compound. The second study of mice (Kimbrough and Linder, 1974) found evidence of nonmalignant lesions in 47% of the mice after an 11 month diet of 300 ppm of Aroclor 1254.

Six studies on rats were reviewed in the Special Panel's report. The first (Kimura and Baba, 1973) found neoplastic nodules in only female rats fed over 1200 mg of PCB in their diet. No mention is made of the second study by Kimura et al. in 1976 which did not find an association between hepatocellular carcinoma and PCBs. The Panel concluded that the study by Ito et al. in 1974 demonstrated that, "all three Kanechlors produced liver changes related to the concentration in the diet." Table 3, presented in support of this statement, contains data on the histopathological findings in the liver of rats given PCBs. At the highest dose (1000 ppm) of the most chlorinated compound (Kanechlor 500), 30.8% developed nodular hyperplasia. Thirty percent and 31.3% of the rats developed nodular

MONS 027426

hyperplasia when fed 1000 ppm of Kanechlor 400 and 500 ppm of Kanechlor 500 respectively. Lower doses and less chlorinated PCBs showed virtually no effect. Noteworthy is the Panel's failure to state that no hepatocellular carcinomas were found in any of the rats including those fed the highest dose-chlorination combination.

In describing (p. 20) the results from Kimbrough et al. (1975), the Panel appropriately acknowledges the substantially increased incidence of hepatocellular carcinomas and neoplastic nodules in experimental animals in this study. They go on to mention that uterine cancers were "also elevated, but not to a statistically significant level". Examination of Table 4 in the Panel's report, which presents Kimbrough's data suggests a more complex picture than the Panel's description. It can be seen that for a number of tumors incidence appears to be reduced, perhaps significantly, in the exposed animals compared to the control animals. In fact, for all tumors other than those of the liver, the incidence was somewhat greater among the control animals than in the animals fed PCBs. PCBs were also not life-shortening as almost twice as many control animals died before the experiment was terminated.

In the study of Norback and Weltman (1985), some significant findings described by the authors are not noted by the Panel. Although the striking sex-related difference in tumor rates is mentioned, the Panel did not mention that the mortality rate was not increased in the PCB exposed group.

An example of a major animal study that is not cited by the authors is that

MONS 027427

by Schaeffer and his colleagues published in 1984. This study reported a significantly increased incidence of neoplastic nodules and hepatocellular carcinomas in Wistar rats receiving Clophen A60 (but not Clophen A30). As noted in a subsequent letter by Young (1985), this study also showed a significantly reduced risk of other tumor types and reduced mortality in both sets of PCB treated animals. Schaeffer et al. considered the protection from neoplasms of the thymus and from nephritis to be the result of PCB-induced alterations in the immune system. It is not clear why the Panel did not include this study; such an omission reduces the confidence in the completeness and balance of the review.

Another study not acknowledged by the Panel was by Kerklivet and Kimeldorf (1977) in which they reported that PCB exposure in rats, "had a significant protective effect on the host in response to the implantation and growth of Walker 256 tumor cells."

The one study of dogs was essentially negative as neither hepatocellular carcinoma nor neoplastic nodules were found in the dogs fed up to 100 ppm of Aroclor 1242, 1254 or 1260.

Five animal studies were reviewed that deal with the cancer-promoting effects of PCBs. As with the studies on carcinogenesis, the effect appears to be limited to the highest dose-chlorinated PCB compounds.

Summary of Experimental Animal Studies

1. The review of the animal studies provided by the Panel is not complete and does not include a balanced perspective on the studies.

MONS 027428

2. In addition to the incomplete presentation of the major findings, the authors also do not provide adequate descriptions or critiques of the conduct of the studies - information that pertains to the overall interpretation and validity of the studies. For example, they do not consistently indicate overall mortality or loss of body weight. Thus it is much more difficult for the reader to evaluate these findings without searching out the original literature.

3. The studies showing an increase in hepatocellular carcinoma incidence show these increases at fairly substantial doses with the most highly chlorinated compounds.

4. Studies showing an increase in liver carcinoma did not show an increase in total tumor incidence, in fact, some show a decrease in the non-liver carcinomas.

5. In two of the studies mortality among the PCB exposed animals was actually decreased.

6. The studies do not, "demonstrate reasonable consistency" as stated in the Panel's report. The studies are inconsistent, and part of this inconsistency possibly stems from comparing the carcinogenicity of the different commercial PCB mixtures. The more highly chlorinated PCB isomers are most carcinogenic, as the Panel's report states. Kimbrough (1987) goes further, stating that it is not certain that the less chlorinated fractions (pentachlorobiphenyls and less chlorinated) cause hepatocellular carcinomas in rodents. This has implications for the

MONS 027429

possible risk of occupational exposures, since the less chlorinated commercial mixtures (e.g. Aroclor 1242, 1254 and 1016) were more commonly used than Aroclor 1260 (Kimbrough, 1987). Of course the less chlorinated commercial mixtures are not devoid of the highly chlorinated congeners, but the concentrations of these congeners are lower in the less-chlorinated mixes (e.g. see Table 2 of the Panel's report).

7. Aroclor 1254 (as opposed to Aroclor 1260) has not definitely been shown to be hepatocarcinogenic in animals. The study most frequently reviewed is that of the National Cancer Institute (1978). There were statistically non-significant increases of hepatocellular carcinomas and hematopoietic cancers in exposed rats. Therefore, the study was equivocal at best and is negative by the criteria set for the NCI bioassays. The Panel criticizes this study on the basis of an increased mortality in the exposed groups, which they state leads to a decreased number of animals at risk for cancer in the dosed groups. While this is true, an alternative argument may also be valid. The excessive mortality in the dosed groups indicates that the doses exceeded the maximum tolerated dose and that therefore the assay is invalid. The NCI guidelines require that the maximum dose of test agent used in a bioassay be one that does not alter the animal's normal longevity unless death is due to tumors (National Cancer Institute 1976). In this NCI report it states, "A Maximum Tolerated Dose (MTD) should be selected for each sex of each strain to be used in the chronic study. The MTD is defined as the highest dose of the test agent given during the chronic study that can

MONS 027430

be predicted not to alter the animals' normal longevity from effects other than carcinogenecity."

8. Still controversial is the relationship of hyperplastic liver nodules to the development of carcinoma. The Panel recognizes that the studies suggesting that the hyperplastic nodules are precursors of malignant tumors are, "not completely definitive". Plaa (1986) cites this interpretation as one of two theories of pathologic progression of liver cancer. Safe (1984) states that these hyperplastic nodules only appear in experimental animals after long exposure to high doses.

Human Morbidity Studies

a. Yusho Disease

Kimbrough (1987) agrees with the Panel's report that the Yusho and Yucheng poisonings can mainly be ascribed to the polychlorinated dibenzofurans (PCFDs) present in the contaminated rice oil. Kimbrough also mentions a highly toxic PCB isomer (3,4,3',4' tetrachlorobiphenyl) as being present in the contaminated oil. Kimbrough notes that this isomer has not been identified in commercial mixtures used in the U.S.

The Yusho and Yucheng episodes do not seem very relevant to the possible carcinogenic properties of PCBs. Kimbrough (1987) states that there is no definitive evidence about cancer rates in the Yusho cohort. The number of cases appearing so far has been small and a sufficient latent period may not have yet elapsed. Furthermore, although PCBs have toxicologic properties qualitatively similar to

MONS 027431

those of polychlorinated dibenzodioxins (PCDDs) and PCDFs, the responses are not identical. In particular 2,3,7,8 dibenzodioxin (TCDD here) can induce tumors at a variety of sites in rodents, while PCBs alone have only induced liver and stomach tumors (Kimbrough, 1985). Furthermore, the exact patterns of enzyme induction of TCDD are mimicked only by a few PCB congeners having specific chlorination patterns (Safe et al., 1985).

b. Skin and Other Cutaneous Tissues

Skin lesions (acneform eruptions, folliculitis and possible skin thickening) appear to be associated with high exposure to PCBs, particularly the higher chlorinated isomers.

c. Blood Chemistry

Several studies have been conducted of workers exposed to various concentrations of PCBs in which serum blood analyses were obtained. The results from these studies are summarized in Table 12 of the Panel's report. The Panel concludes "in considering the overall results, SGOT and GGTP particularly are increased with exposure to PCBs". The results from the SGOT studies given in Table 12 show that only 3 of the 10 studies had significantly positive associations and the studies of GGTP show that 8 of 10 studies had significantly positive association. The Panel concludes that, "most of the results are negative and when positive, the effect is relatively minor."

A number of studies have looked at cholesterol and triglyceride concentration in relation to PCBs. Here the Panel overinterprets the

MONS 027432

results summarized in Table 13. They conclude that, "statistically significant increases in triglycerides and total cholesterol were associated in some studies with increased serum PCB concentrations". However, only 8 of the 20 results in Table 13 are significantly associated.

Furthermore, the Panel notes that "some studies" did not fully control for body mass and it is not clear whether the studies showing a positive association were among those that controlled for body mass. The Panel also does not make it clear that the association can probably be explained by the increased solubility of PCBs in serum with a higher lipid content as suggested by Kimbrough (1987).

d. Liver Abnormalities

The report states that the increased serum liver enzyme levels are of uncertain clinical significance. They find more alarming a report of hepatomegaly in capacitor workers (Maroni et al, 1981), but state that this is an isolated finding. They point out (p.28) that, "Other clinical studies have not reported liver disease of such severity, if at all." It is also important to note that the study of Maroni et al. did not have a control group, nor were the examining physicians blind to the PCB exposure status of the workers. They did, however, find an association between serum PCB levels and the frequency of "abnormal" liver findings as "deduced from symptoms, clinical examination of the liver and laboratory tests."

MONS 027433

e. Cardiovascular Effects

Generally, the associations between PCB exposure and blood pressure have disappeared when the confounding factors of age, sex, smoking and body mass were considered in the analysis. One study (Kreiss et al, 1981) did find an association with blood pressure after contolling for age, sex and body mass. Apparently smoking was not controlled and given the low PCB serum levels (average = 17.2 ppb, range 3.2 - 158), it is unlikely that the association was real.

f. Respiratory Effects

The Panel properly concludes that, "the single study indicating decreased forced vital capacity among PCB exposed workers must be confirmed in other populations".

g. Reproductive Effects

The finding from the studies on reproductive outcomes are weak and unimpressive. The Panel refers to the results as "uncertain" and "suggestive".

h. Cancer Morbidity

One study of cancer among workers is reviewed. The study has not been published in a peer-reviewed journal and apparently no control group was included. However, no case of liver cancer was reported among the exposed workers.

The Panel appropriately points out (p. 31) some of the limitations of the existing morbidity data from occupational exposures and presents

MONS 027434

some clinical/epidemiologic considerations for future studies. They mention that an appropriate group for the study of pregnancy outcomes would be difficult to obtain. Perhaps in this regard, the potential for exposure to spouses or other household contacts of PCB exposed workers should be considered (Fischbein and Wolff, 1987).

Human Mortality Studies

The mortality studies of workers presumably exposed to PCBs are used as the foundation for the recommendations by the Panel. Four epidemiologic mortality studies have been done; one (Brown) was conducted at plants in two different states and hence, the results are presented as if 5 studies have been done. Table 15 provides the characteristics of the populations from the four major studies. Particularly noteworthy from this table is the fact that all the studies were of relatively few people and given the relative rarity of liver cancer in the population, none of the studies would have sufficient statistical power unless the magnitude of the SMR was extremely large, which apparently it is not. Somewhat troubling is the manner in which the data were pooled (meta-analysis), particularly since the panel had to rely on unpublished data provided by the authors to conduct the combined analyses. Tables 16 and 17 of the report provide the observed and expected number of deaths by cause of death for males and females from the "five" studies.

The cohort described in Table 15 for the Nicholson et al. study is not the same as the one used to obtain observed numbers of deaths in Tables 16 and 17. This is a bit misleading and confusing as it suggests that the study

MONS 027435

size was larger than it actually was. Tables 16 and 17 include deaths among study subjects not included in the Brown study. In Table 16, the number of deaths from all causes (43) is less than the number of deaths from cardiovascular disease (53). It is also somewhat surprising that the expected and observed numbers of deaths for all causes are identical for males and females (43 observed and 45.49 expected).

Individually, the results from the studies would be interpreted as showing no association between any cause of death and employment in that particular company. However, when the observed and expected number of deaths are summed over all the studies, a significant ($p = .015$) SMR is found (see Table 18) for death from cancers of the liver, biliary passages and gallbladder based on 7 observed deaths and 2.54 expected. The Panel used a one-sided statistical test when e two-sided test would have been more appropriate. Also, since 21 comparisons were made, the conventional p value of 0.05 is not appropriate because of multiple hypothesis testing.

The Panel attempts to summarize the results within the framework of the Bradford-Hill criteria for assessing the causal significance of observational data. First, with respect to strength of the association, the Panel accepts the fact that since the SMR is statistically significant, this criterion is fulfilled. However, none of the individual studies is significant and, using the meta-analysis, the result is not sufficiently strong to satisfy this criterion (particularly if a more conservative p value and 2 tailed test are used as would be appropriate in this situation). Under consistency, no mention is made of the fact that none of

MONS 027436

the five studies reviewed show a significant association, in fact, the studies are remarkably consistent in that they all fail to demonstrate an association between PCB exposure and liver cancer. With respect to biological plausibility in reference to the supporting evidence from animal studies, the Panel concludes that such support is apparent from the studies reviewed in the document. However, although some of the animal studies do suggest an association, they are far from conclusive as summarized in the earlier sections of this report. Furthermore, no discussion is provided on extrapolating from the doses used in the animal studies to the doses experienced by the workers in the four studies. Nor is any consideration given to the type of PCB compound. This is important because only the more highly chlorinated ones showed a carcinogenic effect with animals. Also, the general issue of extrapolating to humans from animal data is not addressed in the paper. Kimbrough (1987) states, "From empirical observations, humans also appear to be less sensitive to the toxic effects of PCBs. The ability to store these chemicals in adipose tissue may be protective."

With respect to time relationships, the Panel overlooks the fact that 4 of the 7 cases had a duration of exposure of 1 year or less (see Table 22). Furthermore, only two of the cases were actually liver cancer, the others were biliary system or gallbladder cancers and of the 7 cases, 3 were not confirmed. In their analysis, the Panel combines tumors of the liver, biliary duct and gallbladder. The justification given for this grouping is the finding of "preneoplastic lesions" in the biliary tract in a rat

MONS 027437

study. However, there are many differences among these sites in humens with respect to geographic variations in incidence and mortality rates, secular trends, sex ratios and known or suspected risk factors (Fraumeni and Kanton, 1982; Falk, 1982). Thus grouping them is not appropriate.

Absent from the document is any discussion of confounding factors. This is particularly important given the small numbers involved in arriving at the conclusion that an association exists between PCBs and liver, biliary tract and gallbladder cancers. Seven cases were observed, 2.54 expected. It is appropriate to evaluate the potential effect on this association of a confounding factor such as alcohol use or hepatitis B infection (Falk, 1982). A small difference in the prevalence of risk factors between exposed and control groups could be of importance.

Of significance is the fact that no dose-response relationship was found. This would be another issue in evaluating the causal significance of the association. As stated in the document, "as can be seen from Table 24 [should read 23], there is no significant trend with increasing estimated risk when the durations of exposure are periods of employment in the high PCB exposed jobs". The report goes on to state, "however when the deaths in the cohort of Brown are categorized according to total plant employment as other deaths are, the distribution corresponds to an increasing risk of cancer with increasing estimated risk". This is a clear overinterpretation of the results since, as noted by the Panel, the trend is not apparent and the data are not statistically significant.

MONS 027438

Some specific comments regarding the individual mortality studies are given below.

Brown and Jones (1981) and Brown, (1986)

As of the end of February 1988, the Brown study update had not yet appeared in the published literature. The 1981 study was published and available for review.

1. The original study reports that 163 individuals died from 1940-1976, not 160 as stated in the Panel's report.

2. In addition to not observing an increased risk with greater latency, Brown and Jones also did not observe an association with duration of employment.

3. The Panel addresses the possible impact of using U.S. mortality rates, rather than local (county) rates where plants are located, in calculating expected numbers of deaths. With respect to liver and biliary tract cancers, the Panel states that local rates were higher near one plant (Massachusetts), but lower near the other plant (New York). Three out of the 4 liver cancer or biliary tract deaths occurred in the Massachusetts cohort. This cohort also accounted for two-thirds of the total person-years (1981 study). Contrary to the assertion of the Panel, these findings do suggest a possible bias. If the higher local rate of liver cancer where the Massachusetts plant is located were used to calculate the "expected" value rather than the lower U.S. rates, a higher expected number would probably be obtained, which in turn would lower the SMR for these sites.

MONS 027439

4. The original 1981 study found no trend in liver cancer deaths with increasing latency.

5. Brown and Jones (1981) found a trend in mortality from cirrhosis of the liver with increased length of employment which they considered to be "consistent with the notion that PCBs have a toxic effect on the liver." The SMRs increased from 74 for those employed between 3 months and 5 years to 435 for those employed between 15 and 19 years. They state that alcohol consumption is a possible confounder of the association between PCB exposure and liver cancer.

Gustavasson et al. (1986)

Several important aspects of this study were not noted by the Panel.

1. There appears to be an inconsistency in the mortality data presented in Table III in the original article. Total deaths are listed as 21. Under this Total are five major categories of deaths which sum to 27.

2. Neither the study authors nor the Panel provide the person-years of observation for this study, although study power was briefly discussed by the authors.

3. The Panel notes that this study utilized Swedish national rates to obtain expected deaths and that this may have underestimated the deaths expected in this cohort. The Panel then states that use of local rates would have, "only a trivial effect on the overall results of this review". While that may be true, the effects may not be trivial

MONS 027440

regarding the findings of this study. The effects could be quite significant if there are large differences between local and national rates for specific tumor sites.

4. The one liver cancer (actually cancer of the ampulla of Vater) reported from this cohort was not reported as such in the original study which did not have a detailed breakdown by site. The inclusion of this case is based on a personal communication from Gustavasson to the Panel.

Bertazzi et al. (1982) and Bertazzi et al. (1987)

1. According to the Panel and the investigators, the earlier study (1982) included only production workers who had been employed for at least six months between 1946 and 1970. In the updated study (1987), several major changes were made in the definition of the study cohort. First, the eligibility period was extended to 1978. Second, the minimum period of employment was reduced from six months to one week. The authors gave two reasons for this change; one week was apparently the minimum period necessary to obtain reliable data on an employee, and less than six months of employment could produce significant exposure to PCBs. Third, all company employees, not just production employees, were included in the later study. Thus any company employee with at least one week of employment between 1946 and 1978 was included in the study.

2. The study authors did not make a particularly strong case for the changes they made in defining the study cohort, i.e., the inclusion of

MONS 027441

nonproduction employees and those with work histories as short as one week. The evidence cited for significant short-term exposures was a 1954 study of three cases of chloracne in the company among autoclave workers who had worked 4, 6 and 7 months, respectively. Although four other cases of chloracne were diagnosed in 1977 among workers impregnating capacitors with PCBs, the work duration of these workers is not noted and neither their own data nor those of other published studies are presented to support the contention that short-term workers can generally have significant exposures. The inclusion of nonproduction workers was also not well justified. In addition to several air samples of PCBs, a number of workers were assayed for PCBs on their hands and in their blood. Unfortunately, the authors do not adequately specify the locations of the environmental samples, or provide information on how the workers were selected, their occupations or work histories. It was only stated that they represent "typical" exposure conditions. Thus, it is not at all clear that nonproduction workers or very short-term workers had significant exposures to PCBs or that the exposure potential would have been constant over different time periods. The authors do not indicate the proportion of the cohort that fell into these categories.

3. A more significant impediment to interpretation of this study is that the authors did not have available to them detailed employee work histories or job descriptions, and could not classify workers according to work history.

MONS 027442

4. The authors did not find any relationship between mortality and length of employment, latency, or year started. However, as the authors and Panel note, the small number of deaths limit any conclusions that can be drawn.

5. It is somewhat curious that the authors presented characteristics of "selected" cases of cancer deaths in Tables VI and VII for males and females, respectively. In Table VI, they actually presented all 12 male deaths, while in Table VII, they presented only 4 of the 14 female deaths.

Nicholson et al. (1987)

This is an unpublished study, however a draft of the paper was made available for review.

1. The Panel notes that this study was conducted on one of the same plants (Plant 1, New York) that was included in the Brown and Jones study. However, the investigators defined their cohorts quite differently. Brown and Jones defined their study cohort as any worker with at least 3 months of service at any time in an area with high exposure potential - as defined by the company and corroborated by the union and a NIOSH industrial hygiene survey. The Nicholson study cohort consisted of all plant workers with at least five years of service whose employment began before 1954. Furthermore, Nicholson allowed for a 10-year latency; follow-up did not occur until after 10 years from first employment. Because of the different requirements for length of

MONS 027443

employment and time period of employment, it is not surprising that the Nicholson cohort was smaller - 769 workers. The Panel notes that over two-thirds of these workers (521/769) were not included in the Brown and Jones cohort (and it is only data for these workers that is apparently presented in Tables 16 and 17). This finding would suggest that most of the Nicholson cohort did not have the high-exposure jobs as identified by Brown and Jones. In any event, in the absence of more detailed exposure information, it is unclear whether the Nicholson cohort or the Brown and Jones cohort provides a better or adequate study group.

Use of a Meta-Analysis

The application of meta-analysis to retrospective cohort studies is relatively new. It has been more often used for experimental studies where results from a number of randomized trials have been pooled. In these situations a number of criteria had to be met before combining the data from many studies. The Panel's report does not address the appropriateness of conducting the meta-analysis in this situation. There are no formal specifications in the Panel's report for judging that the studies were sufficiently similar to allow pooling. There were sufficient differences among the studies that could invalidate a meta-analysis. The studies were done in different countries (U.S.A., Italy and Sweden) and involved different average durations of employment, different intensities of exposure and different definitions of eligibility for inclusion into the study cohort. Bertazzi et al. did not have work histories and included all plant

MONS 027444

employees who worked one week or more, whereas Brown and Jones included only workers with likely exposure to PCBs with at least three months of work experience. Nicholson et al. included only employees with five years of service and at least ten years of followup (latency).

Inclusion of all relevant articles is important in meta-analysis. The Panel does not state what methods were used to ensure inclusion of all studies. Studies with negative results are less likely to be published than studies with positive results (Sacks et al, 1987). Thus, it is important to provide a well defined framework to survey the research field and identify all studies which address the issue. The Panel presumes to have identified all studies, however, they do not describe a process for conducting the search.

Summary

The panel concludes (p. 49),

"In summary, while only seven deaths from liver and biliary tract cancer occurred, the criteria of Hill for an association with exposure are reasonably well met."

The Hill criteria are not met. The only criterion that has some merit is biological plausibility.

"The association is strong (SMR = 275) and achieves statistical significance."

It is questionable if significance would be attained if a more conservative p value was used (because of multiple hypotheses testing) along with a 2-tailed test. Furthermore, 3 of the 7 cases were not confirmed.

"A finding of excess cancer is present in the workforces of four of the five plants studied; the overall excess did not come from one sporadically high finding."

Of the 5 plants in which males were studied, 2 had no deaths from cancers of the liver, biliary passages and gallbladder, 2 had 1 death and 1 had 2 deaths. Of the 4 plants which included women, 3 had no deaths from these causes and 1 plant had 3 deaths. (The latter is from an unpublished study.) Of the four published studies, Brown and Jones state, "There is no relationship between increasing duration of employment in jobs involving PCB exposure and the risk of mortality due to cancer or cirrhosis of the liver". Bertazzi et al. state, "...both workers who died from cancer of the liver and biliary tract had been employed in the production area, albeit for rather short periods". They later state, "The limitations discussed did not permit a causal assocation to be either proved or dismissed." Gustavsson et al. does not even mention the one liver cancer cited in the Panel's report but do state, "A subgroup of 19 individuals with higher exposure (capacitor fillers and repairers) was analyzed separately but there was no tendency towards an increased mortality or cancer incidence in this subgroup." And finally Nicholson, the chair of the Special Panel concludes his own study with the statement, "The overall results do not indicate any association of PCB exposure with excess mortality for any cause." A final point, the excess did indeed come mainly from one sporadically high finding. Three of the 7 deaths (43%) occurred among females in one of the plants in the Brown and Jones study.

"The concordance of the animal data and the finding of liver tumors in humans exposed to dibenzofurans, structurally similar compounds, adds weight to the human evidence."

MONS 027446

The animal data and their limitations were in this report. Regarding the dibenzofurans (PCDFs) Kimbrough (1987a) states, "The toxicity of individual isomers of the PCBs, PCDDs (dibenzodioxins) and PCDFs varies greatly. The type of effects produced by the same compound and the target organs may differ in different species and may differ for various homologs of this mixture of chemicals. Species variations in response to PCDDs and PCDFs have some similarities, but also some differences. This makes risk estimates extremely difficult."

"The exposure and time relationship of the cancer incidence are in accord with expectations."

No dose response relationship was demonstrated in any of the individual studies nor in the combined data. Four of the 7 cases were employed for one year or less.

"Finally, no other exposure or circumstance could be identified that would provide an alternative explanation for the excess."

It must be pointed out that none of the studies considered other exposures. Important confounding factors such as alcohol use, hepatitis B virus infection or use of oral contraceptives were not considered although Brown and Jones recognized the need to consider alcohol use, particularly since they found a large increase in cirrhosis of the liver.

And finally the Panel concludes,

"Considering all the data, the evidence is strong for a causal association between the excess of these cancers and exposure to PCBs."

MONS 027447

The evidence is not strong and the association cannot be considered causal. "Strong" and "causal" are used to describe associations such as those between cigarette smoking and lung cancer or asbestos and mesothelioma where the data are consistent and persuasive. To use these words to characterize the association between liver cancer and PCB exposure is to distort and grossly exaggerate the weak and inconsistent data that are available. The animal data are suggestive, however, the human data are weak and unconvincing.

MONS 027448

REFERENCES

Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 1987;11:165-76.

Brown DP, Jones M. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health 1981;36:120-9.

Falk H. Liver. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. Philadelphia; WB Saunders, 1982:668-82.

Fischbein A and Wolff, M. Conjugal exposure to polychlorinated biphenyls (PCBs). Brit Indust Med 1987;44:284-6.

Fraumeni JF, Kantor AF. Biliary tract. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. Philadelphia; WB Saunders, 1982:683-91.

Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 1987;10:341-4.

Kerklivet NI and Kimeldorf DJ. Antitumor activity of a polychlorinated biphenyl mixture, Aroclor 1254, in rats innoculated with Walker 256 carcinosarcoma cells. JNCI 1977; 59:951-55.

Kerklivet NI and Kimeldorf DJ. Inhibition of tumor growth in rats by feeding a polychlorinated biphenyl, Aroclor 1254. Bull Environ Contam Toxic 1977;18:243.

Kimbrough RD. Laboratory and human studies on polychlorinated biphenyls (PCBs) and related compounds. Environ Health Persp 1985;59:99-106.

Kimbrough RD. Human health effects of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Ann Rev Pharmacol Toxicol 1987;27:87-111.

Kimbrough RD. Toxicology of halogenated biphenyls, dibenzodioxins and dibenzofurans. ISI Atlas of Science:Pharmacology 1987a;1:139-42.

Kimura NT et al. Polychlorinated biphenyls as a promoter in experimental hepatocarcinogenesis 1976. In: Harbison RD et al. Biological data relevant to the evaluation of carcinoganic risk to humans. August, 1987.

Maroni M, Colombi A, Cantoni S, et al. Occupational exposure to polychlorinated biphenyls in electrical workers. II Health effects. Br J Ind Med 1981;38:55-60.

National Cancer Institute. Guidelines for carcinogen bioassay in small rodents. National Cancer Institute Carcinogenesis Technical Report Series 1976;1. (DHEW Publication No (NIH) 76-801).

MONS 027449

National Cancer Institute. Bioassay of Aroclor 1254 for possible carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series 1978;38. (DHEW Publication No (NIH) 78-838).

Norback DH, Weltman RH. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ Health Perspect 1985;60:97-105.

Plaa GL. Toxic responses of the liver. In: Klaassen CD, Amdur MO, Doull J, eds. Casarett and Doull's Toxicology. New York:Macmillan, 1986:286-309.

Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analyses of randomized controlled trials. N Engl J Med 1987;316:450-5.

Safe S. Polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs); Biochemistry, toxicology, and mechanism of action. CRC Crit Rev Toxicol 1984;13:319-95.

Safe S, Bandiera S, Sawyer T, et al. PCBs: Structure-function relationships and mechanism of action. Environ Health Perspect 1985;60:47-56.

Schaeffer E, Greim H, Goessner W. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol Appl Pharmacol 1984;75:278-88.

Young S. Letter to the editor. Toxicol Appl Pharmacol 1985;78:321-2.

MONS 027450

Attachment I

BIOLOGICAL DATA RELEVANT TO THE EVALUATION OF CARCINOGENIC RISK TO HUMANS

Prepared for
International Agency for Research on Cancer
Review of Carcinogenicity Data
on
Polychlorinated Biphenyls

Prepared by
Dr. Raymond D. Harbison
Dr. Robert C. James
Dr. Stephen M. Roberts

Division of Interdisciplinary Toxicology
University of Arkansas
School of Medicine
Little Rock, Arkansas
U.S.A.

January 1987

MONS 027451

IARC Submission on PCBs

Attachment I

BIOLOGICAL DATA RELEVANT TO THE EVALUATION OF CARCINOGENIC RISK TO HUMANS

1.0 Carcinogenicity and Related Studies In Animals

1.1 Studies in Mice

Nagasaki et al. (1972) initially examined the hepatocarcinogenic effects of Japanese brands of PCB fluids by feeding male mice dietary levels of 100 ppm, 250 ppm, and 500 ppm for 32 weeks. As this particular citation represents a short communication, detailed discussions of the experimental design and histopathological examinations of this investigation were lacking. An increased incidence of liver tumors was found in only one of the treatment groups, those mice receiving the 500 ppm diet of Kanechlor 500, where hepatomas were identified in 58% or 7/12 of the animals. The livers from animals in this group also contained nodular areas and many necrotic foci. In sharp contrast to these findings, no hepatomas and none of these histopathologic changes were observed in animals receiving lower doses of Kanechlor 500 or in any of the animals receiving Kanechlor 400 or Kanechlor 300.

The results of the above study also appear to have been reported in two other journals under Ito et al. (1973a&b). As in the previous study it was reported that male mice of the ddY strain were fed diets containing Kanechlor 300, Kanechlor 400 or Kanechlor 500 at dietary levels of 100, 250 or 500 ppm for 32 weeks. PCBs significantly increased the liver weights of the animals, and at the highest dose of Kanechlor 500 the liver:body weight ratio had increased 3-fold with histopathological examination of the livers revealing a focal hypertrophy in the centrilobular hepatocytes of non-neoplastic areas. Another change observed in all PCB treatment groups, except those receiving 500 ppm of either Kanechlor 500 or 400, was a marked amyloid degeneration of the liver in the space between the sinus endothelium and the hepatocytes. For some reason, the liver tumors in these more recent publications (Ito et al, 1973a&b) have been reclassified, and the tumors reported as hepatomas in the previous communication (Nagaski et al., 1972) are now listed as carcinomas (Ito et al., 1973 a&b). That is, in the group receiving 500 ppm of Kanechlor 500 (originally described as having hepatomas in 7/12 animals) nodular hyperplasia was found in 7/12 animals (58.3%) while 5/12 of the livers (41.7%) now have well-differentiated hepatocellular carcinomas. The carcinoma cells were reported to be comprised of irregularly shaped cells with pyknotic nuclei and occasionally had mitotic nuclei. The reason for changing the classification of these neoplasms from hepatoma to carcinoma is not provided. Of some interest to discussions of the carcinogenic potential of PCBs is the fact that all of the other doses of all three Kanechlors tested failed to produce even nodular hyperplasia. Thus, the tumorigenicity reported was quite specific for the dose and the extent of chlorination of the Kanechlor being tested.

Kimbrough and Linder (1974) examined the effects of PCBs in

MONS 027452

mice and obtained results consistent with those found for the lesser-chlorinated Kanechlors of the preceding study. Groups of 50 male Balb/cJ mice were fed 300 ppm Aroclor 1254 for either 11 months or for 6 months followed by a 5 month recovery period. The authors pointed out that this dietary level was some 2,500 times the Food and Drug Administration's estimate of the average human daily PCB intake from food during the early 1970's. About one-half of the animals in each PCB treatment group died during the first 4 months, but this problem seems to have been unrelated to the PCB treatment as control animals suffered a similar incidence of mortality. Of the 22 mice surviving the 11 month feeding study, all animals had hepatomegaly with the liver representing approximately 25% of their body weight in comparison to the 5.8% liver:body weight ratio measured for the control animals. Adenofibrosis (i.e. cholangiofibrosis) was observed in all 22 livers taken from mice fed PCBs for 11 months, however 13/68 livers taken from control animals had occasional, small areas of necrosis and fibrosis. Of the livers taken from animals receiving 300 ppm Aroclor 1254 for 11 months, the nuclei were enlarged, hyperchromatic and atypical. The cytoplasm was either smooth or vacuolated, and the Kupffer cells contained a brown pigment. Some of these livers had extensive necrosis and fibrosis. In each of the livers, several areas of hepatocytes had been replaced by proliferating epithelial cells which formed ducts and often produced mucus. In addition to these histological changes, 10 hepatomas were found in 9 of these livers. The tumors were described as well circumscribed and surrounded by compressed parenchyma or strands of fibrosis. In the 24 surviving mice fed PCBs for only 6 months followed by a 5 month recovery period, only one liver contained a hepatoma. Yet, liver fibrosis was observed in two-thirds of these animals and hepatocellular necrosis was evident in most of the livers.

1.2 Studies in Rats

Kimura and Baba (1973) exposed 10 male and 10 female Donryu rats to a variable dietary level of Kanechlor 400 for 400 days. The diet initially contained 38.5 ppm and was fed to the animals for 4 weeks; the dietary level was then doubled and provided for the following 8 weeks; the initial dietary level was then increased 4-fold and provided for 3 weeks; it was then increased 8-fold and fed to the animals for another 3 weeks; finally it was increased to 16 times the initial level and fed to the animals for 3 more weeks. This last dietary level (about 616 ppm) was considered too toxic because it caused considerable weight loss, and so the dietary levels were finally decreased to 462 ppm for the remaining 32 weeks of the study. Also complicating the interpretations of this study was the fact that animals died or were sacrificed at various times throughout the experiment and therefore the animals received different total doses of PCBs. In general, the total amount ingested was 1300-1800 mg for the group of males and 1100-1500 mg for the female animals. Microscopically the livers of all of the treated animals contained fatty degenerative changes, and while 6/10 of the livers from female animals had adenomatous nodules,

none of the livers of the male animals contained any nodules. However,the liver nodules observed in the female animals do not appear to be related to the PCB treatment as 2/5 (40%) of the livers from the control female animals also contained adenomatous nodules.

In a second study Kimura et al. (1976) fed 12 female Donryu rats diets containing 400 ppm Kanechlor 400 for 6 months. The estimated dose corresponded to a total of 531 mg of PCBs during this period. Eight of the 12 animals were then sacrificed 590 days after the feeding began. None of these animals developed hepatocellular carcinoma, and 9/12 of the livers were normal in appearance, suggesting that the degenerative changes observed in the previous study are reversible.

Ito et al. (1974) fed male Wistar rats Kanechlor 300, Kanechlor 400 or Kanechlor 500 at dietary levels of 100, 500 or 1,000 ppm for up to 52 weeks. No hepatocellular carcinoma was found in the livers of any of the treated rats. The highest dose of all three Kanechlors did produce a cholangiofibrosis of the liver, but this effect was not observed at the lower doses with any of the Kanechlors. Nodular hyperplasia was observed in 30-40% of the rats exposed to the two highest doses of Kanechlor 500 (i.e. doses of 500 ppm and 1,000 ppm) and in animals receiving a diet containing 1,000 ppm of Kanechlor 400. Oval cell proliferation and proliferation of the bile duct cells were observed in all treatment groups. Hypertrophy of the centrilobular cells was also evident in animals receiving the highest dose of the two most heavily chlorinated PCB mixtures. Fatty changes and fibrosis were also observed in the livers of animals of several of the treatment groups. The fatty changes, hypertrophy and fibrosis of the liver all tended to be present and correlate with the observation of nodular hyperplasia, suggesting that these changes may have been contributory factors.

Kimbrough et al. (1975) published the first major positive study demonstrating that Aroclor 1260 can produce hepatocellular carcinoma in the rat. In this study 200 female Sherman strain rats were fed Aroclor 1260 at a dietary level of 100 ppm for approximately 21 months. There was a statistically significant 6-7% decline in the weight gain of the animals exposed to PCBs in this study suggesting that the dose used approximated the maximally-tolerated dose. The incidence of the histopathological findings from this study are summarized in Table 1. The most consistent histopathologic difference in the PCB treatment group was the finding of hyperplastic or neoplastic nodules in 144/184 (78%) of the livers. More importantly, however, was the finding of hepatocellular carcinoma in 26/184 (14%) of the PCB-treated animals. The tumors were well-differentiated neoplasms of the trabecular type, except in three of the animals which had tumors with a glandular, papillary pattern. Foci of coagulative necrosis were occasionally observed in the cancerous areas, but there was no fibrosis or other evidence of chronic degenerative changes. Tumors in areas other than the liver were not listed as significantly

different, however, in some cases there was a substantial decrease in the tumor incidence of other tissues, e.g.

TABLE 1

Results of Carcinogenesis Bioassay of Aroclor 1260

Organ/Tissue	Tumor Type	Tumor Incidence: Control Animals	Tumor Incidence: Aroclor 1260 Animals
Liver	Hepatocellular carcinoma	1/173	26/184
	Neoplastic nodules	0/173	144/184
	Areas of cytoplasmic alteration	28/173	182/184
Thyroid gland	Parafollicular cell tumor	37/160	18/166
Pituitary gland	Chromophobe adenoma	41/153	28/139
Uterus	Endometrial polyp	18/149	25/163
Mammary gland	Fibroadenoma	17/173	13/184
Lung	Adenoma	2/173	2/184
Ovary	Granulosa theca cell tumor	5/149	0/163

Adapted, in part, from Kimbrough et al. (1975)

as in the case of parafollicular cell tumors of the thyroid. The total incidence of extra-hepatic tumors in the Kimbrough et al. (1975) study was 134/173 (74%) in control animals versus 110/183 (60%) in Aroclor 1260 treated animals. So while PCBs had significantly increased the liver carcinoma incidence, the total tumor incidence (78% in control animals -vs- 74% in Aroclor animals) in PCB-treated animals was actually slightly less than the incidence for control animals. The PCB treatment was also not life-shortening; on the contrary, about twice as many control animals had died for various reasons before the experiment was terminated at 23 months.

Calandra (1976) at the 1975 PCB conference sponsored by the EPA reported the findings of several chronic studies performed by a commercial laboratory for Monsanto. While these studies have never been published the results were recently reviewed by Levinskas (1981). In this study 1,000 rats were divided into ten groups of 100 animals (50 of each sex) and nine of these groups were exposed to Aroclors 1242, 1254 or 1260 at dietary levels of 1, 10 or 100 ppm. Apparently five animals of each sex were sacrificed at 3, 6 and 12 months with about 35 animals to be killed at the end of the

two year study (EPA, 1980). In the animals sacrificed early, only one nodular hyperplasia was observed and it was in the group fed 100 ppm of Aroclor 1260 for 12 months. Mortality in this study was high and approximately one-third of the 105 animals anticipated to be exposed for two years at each dietary level died. Hepatomas were observed in 7/25 livers from animals fed 100 ppm Aroclor 1260, in 4/26 fed Aroclor 1254, 3/19 fed Aroclor 1242, and only 1/168 animals receiving the 1-10 ppm diets. Nodular hyperplasia was twice as prevalent as hepatomas in the high dose animals, particularly in the Aroclor 1254 group.

In 1978 the National Cancer Institute examined the carcinogenic potential of Aroclor 1254 (NCI, 1978). Groups of 24 male and 24 female Wistar rats were fed Aroclor 1254 at dietary levels of 25, 50 or 100 ppm for 105 weeks. Clinical signs of toxicity including hair loss, facial edema and cyanosis occurred by week 72 in the high dose animals and the mean body weights were roughly only 2/3-3/4 that of their respective controls. This decrease in body weight exceeds the no more than 10% weight loss guideline for the estimated maximally tolerated dose that is part of the NCI guideline for cancer bioassays (NCI, 1979). Several histopathologic changes occurred in the livers of animals receiving PCBs that appeared to be related to the PCB treatment, and included hyperplastic nodules, adenomas and hepatocellular carcinomas. Male animals had one hepatocellular carcinoma in the 50 ppm group and only 2 in the 100 ppm group. Although the incidence of the tumors was not significant, the occurrence of proliferative lesions did appear to be dose related. In reviewing this bioassay, the Data Evaluation/Risk Assessment subgroup of the Clearinghouse on Environmental Carcinogens responsible for providing peer review of NCI studies concluded the following :

> "It is concluded that, under the conditions of the bioassay, Aroclor 1254 was <u>not carcinogenic</u> in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats were related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females. Based on the liver proliferative lesions in the treated rats and published reports, it is suggested that Aroclor 1254 may be a tissue promoter."

Morgan et al. (1981) have taken the same tissue sections that originated in the NCI bioassay (NCI, 1978), stained the stomach sections for alkaline phosphatase, and then re-sectioned these tissues for histological evaluation in conjunction with those provided in the NCI study itself. The final incidence of alkaline phosphatase rich areas was 6.4% in controls, 10.4% in animals fed 25 ppm Aroclor 1254, 16.7% in the 50 ppm group, and 35.4% in the 100 ppm group. These changes were most often noted in the pyloric region of the stomach and duodenum (88% of the lesions were found in these areas), suggesting a toxicity specific to the cells of

these areas. Gastric adenocarcinomas comprised six of the 33 total lesions identified in these slices. Three were found in tissues from the 50 ppm treatment group and two in the animal group fed 100 ppm. Thus, the increased incidence of this tumor was not related to the dose of PCBs. The remaining 27/33 lesions identified in this study were described as intestinal metaplasia. The authors concluded that the actual number of lesions they believed should have been observed in the G.I. tract tissue sections of the NCI study was twice the number of lesions reported in the original NCI study. Further, and on the basis of their findings, the authors of this paper concluded that chronic oral Aroclor 1254 exposure may lead to the induction of intestinal metaplasia, and possibly to adenocarcinoma of the glandular stomach of the Fischer 344 rat (Morgan et al., 1981).

Ward (1985) fed Aroclor 1254 to Fischer 344 rats in groups containing 24 male and 24 female animals. The exposure was initiated when the animals were 7 weeks of age and continued for 105 weeks. The animals were exposed to Aroclor 1254 at dietary concentrations of 25, 50 and 100 ppm. There was a dose-related depression of body weight and a decrease in survival. While the survival rate in control animals and in the treatment group receiving 25 ppm was 92% and 83%, respectively, only 58% of the animals receiving the 50 ppm diet and 46% of the animals fed diets containing 100 ppm survived to the end of the bioassay. Focal hyperplasia was of the eosinophilic type and was only observed in PCB-treated animals. If compression was found on two sides of the neoplasm, it was diagnosed as hepatocellular adenoma. A total of 13 eosinophilic, basophilic or vacuolated adenomas were identified. All of these occurred, with one exception, in those animals fed the two higher dietary levels of Aroclor 1254 and the occurrence of adenomas was slightly greater in the male animals (8/13). Only two liver carcinomas were identified, both occurred in male animals receiving the 100 ppm diet. Ward (1985) also reported that Aroclor 1254 increased the incidence of intestinal metaplasia and gastric adenocarcinoma. As in the study of Morgan et al. (1981), the change in adenocarcinoma was neither significant nor dose-related. A significant increase in intestinal metaplasia was only observed in the 100 ppm dose group. Thus, the Ward (1985) study is consistent with the previous NCI bioassay. No statistically significant increase in liver cancer or cancer of other tissues was observed, but the 100 ppm dose does lead to significant intestinal metaplasia. Ward mentions the fact that the liver lesions he observed were predominantly of the eosinophilic type rather than the basophilic type generally observed in the control animals. Based on these changes Ward proposes the idea that these data suggest that PCBs may be capable of initiating liver tumors rather than promoting the background tumor incidence. Yet, in contradiction of his suggestion, Ward also makes note of the fact that inducing agents like PCBs and phenobarbital cause a proliferation of the smooth endoplasmic reticulum (SER) of the liver. This proliferation of the SER gives rise to an eosinophilic appearance of the cytoplasm and provides an obvious explanation for the basophilic to eosinophilic change Ward noted in the cellular

MONS 027457

appearance of the liver tumors of his PCB-treated animals.

Schaeffer et al. (1984) used a total of 432 weanling Wistar rats to examine the effects produced by chronically feeding rats Clophen A60 (equivalent to Aroclor 1260) or Clophen A30 (similar in composition to Aroclor 1242; Brinkman and DeKok, 1980). The study consisted of three groups. Group 1, or the control group of 139 animals which received the normal diet, Group 2 with 152 animals receiving a diet containing 100 ppm of Clophen A30, and Group 3 which consisted of 141 animals fed a diet containing 100 ppm of Clophen A60. After day 801 animals were randomly selected and killed, and the experiment was terminated on day 832. The Clophens used in this study were reported to be free of any chlorinated dibenzofuran contamination, but the level of detection for this analysis was not specified. In those animals necropsied prior to day 800, hepatocellular carcinomas were only identified in the PCB treatment groups, one in Group 2 and a total of 9 were observed in Group 3. This latter number was statistically significant for the Clophen A60 treatment and represented a liver cancer incidence of only 7% for the entire group. In contrast, the incidence of thymoma was significantly reduced by PCB treatment declining from 12% in the control group to 3-4% in the treatment groups. Likewise the total number of the remaining types of neoplasms was significantly reduced by the PCB treatment, with Clophen A60 causing the greatest reduction (from 52 in controls down to 18 in the Clophen A60 group). The final results of this study are shown below in Table 2. The incidence of hepatocellular carcinoma was significantly increased only in those animals receiving the Clophen A60. Thus, the results of this study were consistent with the previous rat studies, i.e. Aroclor 1260, or its equivalent, was reported to have induced hepatocellular carcinoma in rats while the lesser chlorinated PCB mixtures (Aroclors 1254 or lower) were not carcinogenic.

Table 2
Frequency of Hepatocellular Alterations Induced by Chronic Feeding Studies with Clophen A30 and Clophen A60

	# of Foci	Neoplastic Nodules	Hepatocellular carcinoma
Controls (group 1)	6/131 (4.5%)	5/131 (3.8%)	1/131 (0.8%)
Clophen A30 (group 2)	63/130* (48%)	38/130* (29%)	4/130 (3%)
Clophen A60 (group 3)	3/126 (2.4%)	63/126* (50%)	61/126* (48%)

* denotes a significant difference from the control value ($P<0.05$)

In a letter to the editor, Young (1985) reviews the Schaeffer et al. (1984) study, and after analyzing the tumor data with respect to the latency period as well as the general mortality experienced in this study raises several interesting points. The tables generated by Young (1985) are provided below in Table 3.

Table 3

The Incidence of Hepatocellular Carcinoma, Other Neoplastic Lesions, and Mortality by Time Period

Time Interval (days)	Treatment Group: Control	Clophen A30	Clophen A60
	A. Hepatocellular carcinoma		
301-400	0/137	0/150	0/135
401-700	0/111	0/122	0/115
701-800	0/92	1/107	9/85*
	B. Other Neoplasms		
301-400	0/137	1/150	2/150
401-700	32/111	11/122*	9/115*
701-800	30/92	15/107*	7/85*
	C. Incidence and Percentage(%) of Mortality		
101-400	2/139 (1.3%)	2/152 (1.3%)	3/141(2.1%)
401-700	45/137(32.8%)	43/150(28.7%)	23/138(16.7%)
701-800	39/92 (42.4%)	20/107(18.7%)	30/85 (35.3%)
1-800	86/139(61.9%)	65/152(42.8%)*	56/141(39.7%)*

* Different from control value ($P<0.05$), χ^2

Young concludes that the Schaeffer et al. (1984) study demonstrated three things. These are : 1) that a significant increase in hepatocelluler carcinoma occurred only in the oldest animals receiving Clophen A60, 2) that PCB treatment increased the chances of survival of the animals, and 3) that the treatment resulted in a significant decrease in other neoplastic lesions. Given these findings Young implies that it is difficult to conclude, given the balance of the data, whether or not the PCB treatment was in fact detrimental to the rats in light of the fact that the PCB treatment enhanced the rate of survival and decreased the total tumor load of the exposed rats. In essence, he questions the human relevance of tumors which occur only very late in the life of the animal, are

MONS 027459

not life-shortening and do not metastasize to other organs of the body. Thus, to paraphrase Young, one might wonder what effects one should extrapolate to the human exposure conditions given these data and the beneficial effects that are also related to chronic PCB exposure. Lastly, the analysis of Young also calls to question a suggestion made by Schaeffer et al. (1984), which was that the decrease in the incidence of thymoma might be caused by immunosuppressive effects of PCBs. While PCBs cause thymic atrophy at certain doses, any proposed immunosuppressive effect cannot be considered to have a significant clinical impact when the treated animals did not ultimately suffer a greater incidence of morbidity or mortality from either infectious diseases or the cancer induced by this treatment.

The last major rat study to discuss is that of Norback and Weltman (1985). These investigators fed 70 male and 70 female Sprague-Dawley rats a diet containing 100 ppm Aroclor 1260 for 16 months followed by a reduction to 50 ppm for the next 8 months. The animals were then fed a control diet for the remaining 5 months of their lives. All results were compared to a control group which initially consisted of 126 animals, 63 of either sex. At various time points throughout this study two control animals of each sex and three PCB-treated animals of each sex (10 animals in total) were anesthetized with ether and the medial left lobe of the liver of each animal was surgically removed. These tissue samples were taken at 1, 3, 6, 9, 12, 15, and 18 months. At 24 months a similar group was killed and at the end of 29 months all remaining animals were sacrificed. The induction of liver hypertrophy in the centrilobular area of the lobule was evident at the first observation period made one month after the PCB diet was initiated. By the 18th month the liver:body weight ratio had increased from 4% to 12% in the female animals. Macroscopically these investigators noted evidence characteristic of neoplastic nodules near the capsular surface, hepatocellular carcinomas and adenofibrosis. In the PCB-exposed group, the observed lesions appeared in the following sequence : centrilobular hypertrophy at 1 month, foci of cells appeared at 3 months, foci of altered cells in the centrilobular and midzonal regions at 6-9 months, neoplastic nodules appeared at 12 months, trabecular carcinoma was observed after 15 months and adenocarcinoma at 24 months. Simple cystic cholangioma and adenofibrosis appeared in animals 18-23 months after the exposure began. There was no evidence of metastases to the lungs. All trabecular carcinomas had cell arrangements with a glandular, ductal or cystic pattern and all adenocarcinomas had some elements of the trabecular pattern of growth. The lumens of the adenocarcinomas were the apparent result of cellular necrosis.

The incidence of tumors in animals 18 months or older are presented below in Table 4. It should be noted that 7-8 animals sacrificed after 18 months, i.e. at least 15% of the group of animals in which late developing tumors were observed, had undergone a partial hepatectomy during the first 18 months. The effect of this cannot be determined from this experiment, but partial hepatectomy has been used as a promotional stimulus to

increase the incidence of liver tumors induced by other carcinogens. Therefore, it is unfortunate that the authors did not note or describe the possible influence that this might have had on the final tumor incidence measured. Another important factor to consider, and one which is not readily apparent from Table 4, is that almost all of the tumors reported in this study were very late-developing tumors. In Table 1 of their paper, only 4 trabecular carcinomas and only 2 adenocarcinomas had developed between the 18- and 24-month sacrifices. Thus, 35/41 or some 85% of the liver tumors observed in this study developed in the last 25-29 month period of the study. These tumors had not metastasized to other organs, and

Table 4

Incidence of Hepatocellular Neoplasms

	Incidence or % Tumors Observed (The actual number of animals with tumors)		
	Male	Female	Total
A. Control Animals	**(N=32)**	**(N=49)**	**(N=81)**
Trabecular carcinoma	0% (0/32)	0% (0/49)	0% (0/81)
Adenocarcinoma	0% (0/32)	0% (0/49)	0% (0/81)
Number negative	100% (32/32)	98% (48/49)	99% (80/81)
B. Aroclor 1260 Animals	**(N=46)†**	**(N=47)††**	**(N=93)**
Trabecular carcinoma	4% (2/46)	40% (19/47)	23% (21/93)
Adenocarcinoma*	0% (0/46)	51% (24/47)	26% (24/93)
Neoplastic nodule only	11% (5/46)	4% (2/47)	8% (7/93)
Number negative	85% (39/46)	4% (2/47)	44% (41/93)

† The total number includes 8 animals that had received a partial hepatectomy during the first 18 months.

†† The total number includes 7 animals that had received a partial hepatectomy during the first 18 months.

* Animals with both trabecular carcinoma and adenocarcinoma were placed only in the adenocarcinoma group.

none appear to have been life-shortening. Concerning this last aspect, unfortunately no information is given concerning the cause of death for any animals dying early, or concerning the number of animals lost. But from the data supplied it would appear that a number of early deaths occurred only in the group of male control animals. These same observations were also noted by the authors, who stated in the discussion of this paper :

> " Although the tumors met the morphological criteria for malignancy, their biologic behavior was relatively unaggressive. The neoplasms did not metastasise to distant organs nor invade blood vessels. Mortality of the

animals was not increased. The lack of greater morbidity or mortality is likely due to slow progression of the neoplastic process and late appearance and slow growth of the hepatocellular carcinoma."

The authors further noted that it remains to be established whether PCBs have an initiating effect or whether the neoplasms observed result from the promotion of a background incidence of initiated cells.

1.3 Studies In Other Species

Calandra (1976) reported, in summary form, a carcinogenicity bioassay performed in dogs. Groups containing 4 male and 4 female dogs were fed 1, 10 or 100 ppm of Aroclors 1242, 1254 or 1260 for two years. While this exposure interval is for a period of time that is considerably less than the lifetime of the species being tested, no remarkable findings were reported.

1.4 The Effects of PCBs on Other Liver Carcinogens

PCBs have been tested in numerous studies to determine whether they alter the carcinogenicity of other chemicals. The evidence obtained from such studies is often inconclusive, and in several instances similar studies have produced conflicting results. The results of interest include the following:

- A number of studies indicate that PCBs administered after a carcinogenic dose of a liver carcinogen enhance the incidence of tumors. Nishizumi (1976) found that Kanechlor 500 promotes liver tumors initiated by diethylnitrosamine. Kimura et al. (1976) demonstrated that Kanechlor 400 can promote the liver cancer induced by 3'-methyl-4-dimethylaminoazobensene (MeDAB). Ito et al. (1978) initiated liver tumors with N-2-fluorenylacetamide and then increased tumor incidence by feeding the rats diets containing 1,000 ppm of PCBs. Preston et al. (1981) have reported that Aroclor 1254 with or without polychlorodibensofuran contaminants can promote the liver cancer initiated by diethylnitrosamine. Osterle and Deml (1984) demonstrated that this effect can be produced in weanling rats, although the immature animal is less sensitive. Deml et al. (1983) have also found that an initial PCB pretreatment to increase oxidative metabolism, followed later by PCB administration for its promotional effects, increased the number of rat liver preneoplastic islands. Similarly, Pereira et al. (1982) demonstrated that Aroclor 1254 promoted the number of diethylnitrosamine-induced enzyme-altered foci in rat livers. In contrast to all of the above studies, Hendricks et al. (1980) found that PCBs did not promote the incidence of liver tumors induced by aflatoxin B_1 in trout, even though the trout were fed a diet containing PCBs for 12 months after the

MONS 027462

aflatoxin B_1 exposure.

- Loury and Byard (1983) observed that Aroclor 1254 enhanced the DNA repair response of amino acid pyrolysate mutagens in primary hepatocyte culture when the PCBs were given three days prior to cell isolation. Thus, it appears that these effects are related to a PCB enhancement of oxidative metabolism. In contrast, Nesnow et al. (1981) found that Aroclor 1254 did not enhance the benzo(a)pyrene-mediated transformation of C3H10T1/2CL8 mouse embryo fibroblasts even though a number of other chemicals known to induce drug metabolism were positive in this test.

- PCB exposure in utero and during nursing protected Wistar rats from diethylnitrosamine-induced liver tumors (Nishizumi, 1980). Likewise Kimura et al. (1976) found that PCBs given before or during MeDAB exposure decreased the incidence of MeDAB-induced liver cancer. Similarly, Makiura et al. (1974) have shown that the co-administration of PCBs with the liver carcinogens MeDAB, N-2-fluorenylacetamide and diethylnitrosamine decreases tumor incidence. Trout fed diets containing PCBs prior to their exposure to aflatoxin had a reduced frequency of liver tumors induced by the aflatoxin (Hendricks et al. 1977). This effect is perhaps explained by Stott and Sinnhuber (1978) who demonstrated that PCBs reduced the bioactivating ability of trout microsomal fractions used to test the mutagenicity of aflatoxin B_1.

- In dermal initiation-promotion assays PCBs have been found to diminish the initiating activity of certain skin carcinogens and to be devoid of any promoting activity (DiGiovanni et al., 1977; Berry et al., 1978). Similarly Hayes et al. (1985) examined the effects of PCBs on the proliferating hepatocytes in livers of young animals or adult animals after partial hepatectomy. They concluded that short-term PCB exposures do not have an initiating action in an *in vivo* assay that detects both hepatic and extra-hepatic initiating carcinogens.

- In contrast to its reportedly adverse effects on the immune system, Kerklivet and Kimeldorf (1977a&b) demonstrated that PCBs administered either in the diet or by injection reduced the size of Walker 256 carcinosarcomas transplanted to rats and increased the lifespans of the animals.

It is concluded from these studies that the liver hypertrophy induced by PCBs can and does enhance the carcinogenic response of initiating hepatocarcinogens if the PCBs are given some time after the liver cells have been initiated by the other chemical. However, this effect has been demonstrated for phenobarbital and is

no doubt also true for most other liver enzyme inducing chemicals that produce a hypertrophy or hyperplasia of the liver. In contrast to its promotional effects on liver carcinogens known to be initiators, PCBs also act as anticarcinogens when administered prior to the exposure of an initiating carcinogen. This effect is most probably the result of PCB induction of liver metabolism which then acts to decrease the carcinogenic effects of a number of chemicals by increasing their degradation and elimination.

2.0 Epidemiological Studies of PCB Exposure and Cancer Mortality

Published epidemiological studies addressing the carcinogenic potential of PCBs have been confined to two cohorts, both consisting of employees of plants where PCBs were used in the manufacture of capacitors. [Note : Bahn et al. (1976), in a letter to the editor, reported an analysis of eight deaths among 92 research and development workers at a refinery, and suggested an association between PCB exposure and incidence of malignant melanoma. The extremely limited size of their cohort, the inability to adequately assess exposure of the cohort to other, potentially carcinogenic substances or other known risk factors, and the inconsistency of their observations with the results from the two larger cohorts, precludes any utility of this report in the assessment of the human carcinogenicity of PCBs.]

Brown and Jones (1981) have published a retrospective cohort mortality study of employees from two plants. Minimal exposure period to PCBs was three months, and the types of PCBs used were Aroclors 1016, 1242, and 1254. Workers who had potential exposure to trichloroethylene, which was also used in both plants, were excluded from the cohort. Of the 2567 employee cohort, 163 were known to be deceased and the vital status of 55 (2%) was unknown.

Higher-than-expected incidences of cancer in the rectum (primarily among females in Plant #2) and liver were noted, although the differences were not statistically significant. The overall incidence of malignancies observed was slightly less than expected. None of the causes of death showed a clear association with latency, and no relationship was observed between the duration of employment in jobs involving PCB exposure and risk of mortality due to cancer. The causes of mortality and incidences of specific malignant neoplasms are summarised in Table 5.

The study of mortality in this cohort has recently been updated, with the number of deceased increasing from 163 to 295 (Brown, unpublished data). There were no additional deaths from cancer of the rectum which brought the observed incidence of this form of neoplasm closer to the expected value. The number of observed malignancies of the liver was significantly greater than expected. However, a number of these malignant neoplasms (3/5) appear to have been the result of metastasis from other sites.

MONS 027464

Thus, like the rectal cancer the standard mortality rate (SMR) for liver cancer originating in the liver has been substantially lowered by this larger cohort. A higher-than-expected incidence of neoplasms was not noted for any other tissue. The overall incidence of malignancies observed was less than expected. There was no apparent relationship between duration of employment in "PCB-exposed" jobs or total employment and cancer mortality of any type.

Table 5. Major Causes of Death for Plant Workers Exposed to Aroclor 1016, 1242, and 1254

Causes of Death	Observed/Expected	Standard Mortality Rate
	All Causes of Mortality	
All malignant neoplasms	39/43.79	(89)
Diseases of nervous system	11/12.55	(88)
Diseases of circulatory system	60/62.93	(95)
Accidents	13/18.29	(71)
All other causes	40/44.79	(80)
Total mortality for all causes	163/182.35	(89)
	Malignant Neoplasms	
Cancer of stomach	1/1.66	(60)
Intestine	4/4.03	(99)
Rectum	4/1.19	(336)
Liver	3/1.07	(280)
Pancreas	1/1.90	(53)
Respiratory	7/7.98	(88)
Breast	7/6.84	(102)
Lymphatic	2/4.34	(46)
Other	10/14.78	(68)

Source: Brown and Jones (1981)

The first study of the second major cohort was reported by Bertazzi et al. in 1981. Inclusion in the cohort was limited to workers in the production department who had been employed for at least six months. There were a total of 1310 workers included in the study, and exposure was primarily to Aroclor 1254 and Pyralene 1476. While some members of the cohort were also exposed to trichloroethylene, alkylbenzene, and epoxy resins, the number was stated to be few. A total of 27 deaths were observed in the cohort between 1954 and 1978. The overall incidence of cancer observed was significantly higher than expected (14 versus 5.65 expected), contributed primarily by elevated (though not statistically significant) incidences of neoplasms of the digestive organs and

MONS 027465

lymphatic and hematopoietic systems.

Bertazzi et al. (in press) have recently published an update of their study of PCB-exposed capacitor workers with a modified cohort. Non-production workers at the plant were added to the cohort, and the minimum period of employment was reduced from six months to one week. The size of the cohort was consequently increased to 2100, and the number of deceased to 64. The results from male and female workers were analyzed separately, and are summarized in Tables 6 and 7.

For males, mortality from cancer was significantly greater than expected (14 versus 5.5 expected). Among specific tissues, the observed incidence of neoplasms of the GI tract was significantly higher than expected, and hematologic neoplasms were also greater than expected but not statistically significant. Overall mortality was only slightly greater than expected. Among females, higher-than-expected incidences of overall mortality, mortality from cancer, and incidence of hematologic neoplasms were observed. These differences were of statistical significance when the cohort was compared to local mortality rates but not national mortality rates. While neoplasms were grouped by organ-system for statistical analysis, specific tumor sites were noted. Among both male and female members of the cohort, there was one case of liver cancer and no cases of rectal cancer. There was no apparent association between duration of exposure, latency, and year of first exposure for any of the causes of mortality.

Table 6. Mortality From Selected Causes of Male Workers Exposed to PCB

Estimates		Reference Cohort: National Mortality Estimates		Local Mortality	
Cause of death	Observed	Expected	SMR	Expected	SMR
All causes	30	27.8	108	29.8	101
Malignant tumors	14	5.5	253[a]	7.6	183[b]
Cancer of G.I. tract	6	1.7	346[c]	2.2	274[d]
Lung cancer	3	1.2	250	1.6	187
Hematologic neoplasms	3	0.8	375	1.1	263
Cardiovascular disease	8	7.9	101	9.4	95
Accidents	6	6.8	88	5.8	103

Confidence limits (95%) [a] 144-615 [b] 104-300 [c] 141-721 [d] 112-572

MONS 027466

Table 7. Mortality From Selected Causes of Female Workers Exposed to PCB

Cause of death	Observed	Reference Cohort: National Mortality Estimates Expected	SMR	Local Mortality Estimates Expected	SMR
All causes	34	25.8	132	16.5	206[a]
Malignant tumors	12	7.7	156	5.3	226[b]
Hematologic neoplasms	4	1.5	266	1.1	377[c]
Cardiovascular disease	2	4.7	42	3.0	66
Accidents	9	4.0	225	4.0	225
Confidence limits (95%)	[a]= 145-285 [b]= 123-385	[c]= 115-677			

From Bertazzi et al., 1986

3.0 Other Relevant Human Data

3.1 Health Effects Information from Accidental Ingestion

In 1968, the ingestion of PCB-contaminated rice oil in Japan resulted in an outbreak of chloracne and other symptoms which were later termed "Yusho". A similar large-scale incident of ingestion of contaminated rice oil occurred approximately ten years later in Taiwan with similar symptoms. The most common symptoms observed in rice oil poisoning victims included increased discharge from the eyes, swelling of the eyelids, accompanying visual disturbances, fatigue and malaise, headache, and symptoms suggestive of peripheral neuropathies (numbness of the limbs and pruritis) (Higuchi, 1976; Okumra, 1984; Lu and Wong, 1984). Other notable symptoms reported included acneform lesions and hyperpigmentation. The incidence of hyperpigmentation was high (9/10) among offspring born to mothers pregnant during ingestion of the contaminated rice oil (Higumhi, 1976). This hyperpigmentation gradually faded over the 2-5 months after birth. Developmental tooth and bone defects were noted among some of the offspring (e.g. eruption of teeth at birth, larger-than-usual frontal and occipital fontanelles, and maintenance of a wider sagittal suture than usual). However, postnatal physical and mental development of infants born to contaminated rice oil-exposed mothers paralleled that of healthy infants (Higuchi, 1976).

While it was originally assumed that the rice oil was contaminated with only PCBs (Kanechlor 400), subsequent analysis revealed that there was also extensive contamination with

MONS 027467

polychlorodibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Studies in animals have clearly indicated that PCDFs are more toxic than PCBs, and a number of lines of evidence support the contention that the adverse health effects suffered by the rice oil poisoning victims were a result of PCDF rather than PCB exposure. First, the concentrations of PCBs measured in patients with symptoms of Yusho were substantially lower than those observed in a number of studies of healthy, occupationally-exposed workers (Kunita et al, 1984; Masuda et al, 1985). The occupational studies have also shown workers to have undetectable or minimally-detectable concentrations of PCDFs (Kashimoto et al, 1985), while rice oil victims in Japan and Taiwan had significant concentrations of PCDFs, including a number of extremely toxic isomers. These human observations are supported by a study in which monkeys were fed PCBs with levels of PCDF and PCQ contamination similar to that of the Yusho oils (Kunita et al, 1984). Monkeys fed this diet developed dermatologic symptoms resembling those seen in patients with Yusho. Monkeys fed PCBs without PCDF/PCQ contamination, or fed PCQs alone, did not develop dermatologic lesions. Collectively these observations have led to the conclusion that the symptoms experienced by the rice oil poisoning victims were the result of PCDF rather than PCB exposure (Kurstsune, 1980; Kashimoto et al, 1981; Drill et al, 1982; Masuda et al, 1982; Masuda and Yoshimura, 1984; Chen et al, 1984; Kunita et al, 1985; Miyata et al, 1985, and Bandiera et al, 1984).

3.2 Health Effects Information from Environmental Exposure

A number of studies have attempted to measure health effects from environmental exposure to PCBs. The most common source of environmental exposure in these studies was the consumption of Lake Michigan fish (e.g. Humphrey, 1980; Fein et al, 1984; Kreiss et al, 1981; Smith, 1983), although the results from other sources of environmental exposure have also been studied (e.g. Baker et al, 1980). The results from these studies have generally been negative. Interpretation of the meaning of the few positive observations has been hampered by either the absence of a control population matched for known risk factors for the parameter studied, a strong positive correlation between PCB body burden and the body burden of other halogenated organics, or the inability to demonstrate increased PCB body burden in the "exposed" population compared with background body burdens in "non-exposed" controls. The absence of these apparent adverse effects in studies of workers with much higher PCB exposures (see below) casts further doubt on the significance of these findings.

3.3 Health Effects Information from Occupational Exposure

With few exceptions, individuals with the largest and longest exposure to PCBs are found in the occupational setting. For this reason, the study of occupational exposure to PCBs is probably the best source of information regarding their health effects in humans.

A population of 326 workers employed at two capacitor manufacturing plants had been the most studied, and a number of reports concerning their health have appeared in the literature. Though this population had been exposed to Aroclor 1016 during the most recent two year period prior to the initial study (and to a lesser extent Aroclor 1221), the long-term exposure was primarily to Aroclors 1242 and 1254 (Fischbein et al, 1979). Duration of exposure to PCBs was substantial, as 40% of the workers had been employed for 20 years or longer. Air levels of PCBs varied widely throughout the plants, ranging from 0.007 mg/m^3 to 11.0 mg/m^3 (Fischbein et al, 1982). Wolff et al (1982) analyzed 290 plasma samples and 61 adipose tissue samples from these workers and found plasma concentrations of lesser chlorinated PCBs ranging from 6-2350 ppb, plasma concentrations of higher chlorinated PCBs ranging from 0-546 ppb, adipose levels of lesser chlorinated PCBs of 0.6-414 ppm, and adipose levels of higher chlorinated PCBs from 1-165 ppm. Approximately half of the population had a history of dermatologic symptoms, rash being the most common. A history of non-adolescent acne, a symptom considered characteristic of PCB exposure, was reported by 12% of the workers (Fischbein et al, 1982). Edema of the upper eyelid, eye discharge, and enlargement of the Meibomian glands, common symptoms among patients with Yusho, were each found in 7% or less of the occupationally-exposed workers (Fischbein et al, 1985). Warshaw et al (1979) studied respiratory function in 243 of the workers and found that 14% had abnormal forced vital capacity. From an extensive examination of clinical chemistry parameters in the PCB-exposed worker population, Fischbein et al (1979) concluded

"_ *there was a paucity of abnormal results in the biochemical studies. Similar findings were noted in the results of the hematologic tests* _ ".

Other occupationally-exposed populations have also been studied, and have been included in a recent review by Gaffey (1983) of the human health effects of PCBs. Gaffey, in surveying the human PCB literature, classified health effect observations into five categories: dermatologic findings, liver function, fat metabolism, blood and blood pressure, and symptoms, illnesses, and other conditions. Which respect to each of these categories, the following observations and conclusions were noted:

> Dermatological effects: Of 11 studies of PCB-exposed workers which reported dermatologic findings, dermal symptoms were noted in all 11. Correlation of dermal symptoms with blood PCB concentrations were generally poor or non-existent. However, collectively the evidence strongly suggests that chloracne may occur when PCB blood levels exceed 150-200 µg/ml.
>
> Liver function: Some abnormality in liver function indicated by a change in one or more relevant clinical chemistry parameters, was observed in five of seven studies of occupational exposure to PCBs. [Though not mentioned by Gaffey, it should be noted that while differences in some parameters indicative of liver

MONS 027469

function were observed to be statistically significant in some of these studies, these differences were uniformly quite small. Further, with chemical-induced hepatotoxicity one would expect to find a consistent pattern of abnormalities among overlapping indices of liver function. No such consistant pattern was observed.) In no case was the abnormality associated with any measurable adverse health effect. The remaining two studies found no evidence of liver abnormalities. A ninth study found evidence of induction of drug metabolism among PCB-exposed workers (Alvarez et al, 1977).

Fat metabolism: There appears to be a correlation between serum triglycerides and PCB exposure in most studies. Results concerning cholesterol are equivocal, with one study showing an increase, one a decrease, and three no change. Conflicting results have also been observed with HDL-cholesterol. Changes in fat metabolism produced by PCBs, if they exist, do not appear to be of clinical significance.

Blood and blood pressure: None of the five studies which examined blood chemistry noted abnormalities associated with PCB exposure. One study of PCB-exposed workers measured blood pressure, but found no association with PCBs.

Symptoms, illness, and other conditions: Five studies report a variety of symptoms among PCB-exposed workers. Most of these symptoms appear to be unrelated to PCB exposure. None of the reports have found significant clinical effects to be associated with PCB exposure.

3.4 Summary of Non-cancer Human Health Effects of PCBs:

PCBs appear to be of low potency in producing adverse human health effects. Among workers with demonstrated high body burdens of PCBs, the only consistently demonstrated clinical finding is dermatological abnormalities. Though one study has found evidence for hepatic ensyme induction in humans, there is no compelling evidence for PCB-induced liver injury despite relatively high levels of exposure. A number of subjective and objective symptoms have been reported for workers exposed to PCBs, and a variety of such symptoms would be expected in examining any population. The appearance of symptoms usually does not correlate with PCB levels or exposures, and no symptom or symptom type (other than dermal) is prominent when the studies are considered collectively. Exposure to PCBs highly contaminated with PCDFs may lead to significant symptomology, but these effects appear to be due to the more toxic PCDFs.

4.0 SUMMARY OF DATA REPORTED AND EVALUATION

4.1 Evaluation of Animal Evidence for Carcinogenicity of PCBs

The investigation of PCBs' carcinogenic potential in mice is limited to two short studies, while some ten studies have been reported using various strains of rat. The PCB mixtures tested thus far are : 1) in mice - Kanechlor 300, Kanechlor 400, Kanechlor 500 and Aroclor 1254; and 2) in rats - Kanechlor 300, Kanechlor 400, Kanechlor 500, Clophen A30, Clophen A60, Aroclor 1254 and Aroclor 1260.

PCBs have been found to be tumorigenic in mice with Aroclor 1254 producing hepatomas after 11 months of exposure and Kanechlor 500 (similar in composition to Aroclor 1254) inducing hepatocellular carcinomas after 8 months of exposure. These lesions were shown to be reversible and specific for the dose (500 ppm) and chlorination of the PCB mixture.

In rats, Aroclor 1260 or its equivalent, Clophen A60, have produced hepatocellular carcinomas in three studies at doses of approximately 100 ppm, a dose which appears to represent the maximally tolerated dose for rats. A review of these three studies indicates that the tumors occur very late in the life of the animal, with a significant incidence of tumors only beginning to appear after about two years of exposure. Of interest is the fact that in all three studies the PCB treatment, while increasing the incidence of liver cancer, did not increase the total tumor incidence. The total tumor incidence was not increased in these studies because in each case the incidence of other tumor types had been significantly decreased. This suggestion of antitumor activity of PCBs has also been demonstrated in a study examining the effect of PCB exposure on the final tumor incidence in animals following the transplantation of the Walker 256 sarcoma. The effects of chronic PCB-treatment was not life-shortening, and in fact in two of the studies the morbidity and mortality of the animals was actually decreased by PCB treatment. Furthermore, while the tumors are described as malignant, i.e. hepatocellular carcinomas, in none of the three studies did the liver tumors metastasize to other organs even though metastases would be expected if the tumors were malignant. So from these studies it is evident that PCB-treatment does not increase the total cancer risk in these animals, rather it shifts the incidence of the type of tumors observed by significantly decreasing some tumor types while enhancing the incidence of liver tumors. Lastly, PCB mixtures of lesser chlorination, i.e. Aroclor 1254 and Clophen A30 (similar in composition to Aroclor 1242, see table 1.4, page 8, of Brinkman and DeKok, 1980), have been examined in at least three separate studies and found not to be carcinogenic. Thus, conclusions to be drawn from the rat data, like the mouse data, are specific for the dose and degree of chlorination of the PCB mixture being tested.

Because PCBs produce liver hypertrophy, they enhance the

MONS 027471

between PCB exposure and these malignancy types cannot be considered strong, however, in that: 1) no cases of rectal cancer were observed after the initial report, suggesting that this increased rate was anomalous, 2) the number of cases of liver cancer observed in this study is not appreciably greater than expected when examined without the total number used by Brown which includes those liver cancers that have metastasized from other organs, 3) in comparison, the study by Bertazzi et al. found only one case of liver cancer and no cases of rectal cancer in their cohort, and 4) the absence of a clear association with latency or relationship with duration of exposure.

The primary sites of neoplasms contributing to the higher-than-expected cancer mortality rates in the Bertazzi studies were located in the digestive system and the hematopoietic and lymphatic systems. These were not increased in the larger cohort reported by Brown. Further, in the Bertazzi cohort, there was no evidence of latency or relationship between cancer mortality and exposure to PCBs. It should also be noted that in the larger of the two subdivisions of their cohort, the female workers, differences in incidences of causes of death presumably unrelated to PCB exposure (viz., increases in accidental death and decreases in deaths from cardiovascular disease) were of similar magnitude as increases in death from malignant tumors. This suggests, at least for this group, that other confounding variables may exist.

In summary, epidemiological evidence for human carcinogenicity of PCBs is at present weak and mostly negative. As such, until larger epidemiological studies can be completed, the data must be considered *inadequate to characterize PCBs as human carcinogens*.

4.3 Evaluation

Aroclor 1260 /Clophen A60/PCB 60% chlorine

There is *sufficient evidence* of *limited human relevance* for the carcinogenicity of Aroclor 1260 in animals.

The human evidence for carcinogenicity of this compound is *inadequate* .

Aroclor 1254 /Kanechlor 500

There is *inadequate evidence* for the carcinogenicity of Aroclor 1254 in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

Aroclor 1248/Kanechlor 400 :

There is *no evidence/insufficient evidence* for the carcinogenicity of Aroclor 1248 in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

MONS 027472

aphen A10/Kanechlor 300/Aroclor 1242 :

There is either *no evidence* or *insufficient evidence* for the carcinogenicity of these mixtures in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

MONS 027473

REFERENCES

Alvares, A.P. et al. 1977. Alterations in drug metabolism in workers exposed to polychlorinated biphenyls. Clin. Pharmacol. Ther. 22:140.

Bahn, A.K. et al. 1976. Melanoma after exposure to PCBs. New Engl. J. Med. 295:450.

Baker, E.L. et al. 1980. Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am. J. Epidemiology 112:553.

Bandiera, S. et al. 1984. Comparative toxicities of the polychlorinated dibenzofuran (PCDF) and biphenyl (PCB) mixture which persists in Yusho victims. Chemosphere 13(4):507.

Berry, D.L. et al. 1978. Lack of tumor-promoting ability of certain environmental chemicals in a two-stage mouse skin tumorigenesis assay. Res. Commun. Chem. Pathol. Pharmacol. 20:101.

Bertazzi, P.A. et al. In press. Cancer mortality of electrical workers exposed to PCB's. Am. J. Ind. Med.

Bertazzi, P.A. et al. 1981. Mortality study of male and female workers exposed to PCBs, presented at the International Symposium on Prevention of Occupational Cancer Helsinki, Finland.

Brinkman, U.A. Th. and A. DeKok. 1980. Production, properties and usage. In: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products (ed. R.D. Kimbrough) Elsevier, New York, NY, p. 1-40.

Brown, D.P. 1986. Mortality of workers exposed to polychlorinated biphenyls - An Update. (under revision)

Brown, D.P. and M. Jones. 1981. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch. Environ. Health. 36:120.

Calandra, J.C. 1976. Summary of toxicological studies on commercial PCBs. In: Proceedings of the National Conference on Polychlorinated Biphenyls. USEPA report 560/6-75-004.

Chen, P.H.S. et al. 1984. Polychlorinated biphenyls, dibenzofurans, and quaterphenyls in the toxic rice-bran oil and PCBs in the blood of patients with PCB poisoning in Taiwan. Am. J. Ind. Med. 5:133.

Deml, E. et al. 1983. Benzo(a)pyrene initiates enzyme-altered islands in the liver of adult rats following single pretreatment and promotion with polychlorinated biphenyls. Cancer Lett. 19:301.

DiGiovanni, J. et al. 1977. Tumor-initiating ability of 2,3,7,8-tetrachlorodibenzo-p-dioxin and Aroclor 1254 in the two stage system of mouse skin carcinogenesis. Bull. Environ. Contam. Toxicol. 18:552.

Drill, V.A. et al. 1982. Comments and Studies on the use of Polychlorinated Biphenyls in Response to an order of the United States Court of Appeals for the District of Columbia. Drill, Freise, Hays, Loomis and Shaffer Inc., Consultants in Toxicology, Arlington, VA.

EPA (Environmental Protection Agency). 1980. Ambient Water Quality Criteria for Polychlorinated Biphenyls. EPA 440/5-80-068, PB81-117798.

Fein, G.G. et al. 1984. Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age. J. Ped. 105(2):315.

Fischbein, A. et al. 1979. Clinical findings among PCB-exposed capacitor workers. N.Y. Acad. Sci. 320:703.

Fischbein, A. et al. 1982. Dermatological findings in capacitor manufacturing workers exposed to dielectric fluids containing polychlorinated biphenyls (PCBs). Arch. Environ. Health 37:69.

Fischbein, A. et al. 1985. Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls (PCBs). Brit. J. Indust. Med. 42:426.

Gaffey, W.R. 1983. The epidemiology of PCBs. In: PCBs: Human and Environmental Hazards. F.M. D'Itri and M.A. Kamrin (Eds.), Butterworth Publ., Woburn, MA.

Hayes, M.A. et al. 1985. Influence of cell proliferation on initiating activity of pure polychlorinated biphenyls and complex mixtures in resistant hepatocyte *in vivo* assays for carcinogenicity. J. Natl. Cancer Instit. 74:1037.

Hendricks, J.D. et al. 1980. Null effect of dietary Aroclor 1254 on hepatocellular carcinoma incidence in Rainbow trout (Salmo gairdneri) exposed to aflatoxin B_1 as embryos. J. Environ. Pathol. Toxicol. 4:9.

Hendricks, J.D. et al. 1977. Inhibitory effect of a polychlorinated biphenyl (Aroclor 1254) on aflatoxin B1 carcinogenesis in rainbow trout. J. Natl. Cancer Instit. 59:1565.

Higuchi, K. 1976. PCB Poisoning and Pollution, Academic Press, New York, N.Y.

Humphrey, H.E.B. 1980. Evaluation of humans exposed to halogenated biphenyls. Am. Chem. Soc. Div. Environ. Chem. Preprints 20(2):272.

Ito, N et al. 1978. Enhancing effect of chemicals on production of hyperplastic liver nodules induced by N-2-fluorenylacetamide in hepatectomized rats. Cancer Res. 41:3071.

Ito, N. et al. 1974. Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann 65:545.

Ito, N. et al. 1973a. Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effects on liver tumors induced by benzene hexachloride. J. Natl. Cancer. Inst. 51:1637.

Ito, N. et al. 1973b. Interactions of liver tumorigenesis in mice treated with technical polychlorinated biphenyls (PCBs) and benzene hexachloride. In: New Methods in Environmental Chemistry and Toxicology, p. 141.

Kashimoto, T. et al. 1981. Role of polychlorinated dibenzofuran in Yusho (PCB poisoning). Arch. Environ. Health. 36:321.

Kashimoto, T. et al. 1985. PCBs, PCQs and PCDFs in blood of Yusho and Yu-Cheng patients. Environ. Health Persp. 59:73.

Kerklivet, N.I. and D.J. Kimeldorf. 1977a. Antitumor activity of a polychlorinated biphenyl mixture, Aroclor 1254, in rats innoculated with Walker 256 carcinosarcoma cells. J. Natl. Cancer Instit. 59:951.

Kerklivet, N.I. and D.J. Kimeldorf. 1977b. Inhibition of tumor growth in rats by feeding a polychlorinated biphenyl, Aroclor 1254. Bull. Environ. Contam. Toxicol. 18:243.

Kimbrough, R.D. and R.E. Linder, 1974. Induction of adenofibrosis and hepatomas of the liver in Balb/cJ mice by polychlorinated biphenyls (Aroclor 1254). J. Natl. Cancer Instit. 53:547.

Kimbrough, R.D. et al. 1975. Induction of liver tumors in Sherman strain rats by polychlorinated biphenyl Aroclor 1260. J. Natl. Cancer Inst. 55:1453.

Kimura, N.T. et al. 1976. Polychlorinated biphenyls as a promoter in experimental hepatocarcinogenesis. Z. Krebsforsch. Klin. Onkol. 87:257.

Kimura, N.T. and T. Baba, 1973. Neoplastic changes in the rat liver induced by polychlorinated biphenyl. Gann 64:105.

Kreiss, K. et al. 1981. Association of blood pressure and polychlorinated biphenyls. J. Am. Med. Assoc. 245:2505.

Kunita, N. et al. 1984. Causal Agents of Yusho. Am. J. Ind. Med. 5:45.

MONS 027476

Kunita, N. et al. 1985. Biological effect of PCBs, PCQs and PCDFs present in the oil causing Yusho and Yu-Cheng. Environ. Health Persp. 59:79.

Kuratsune, M. 1980. Yusho. In: Halogenated Biphenyls, Triphenyls, Naphthalenes, Dibenzodioxins and Related Products, R. Kimbrough (ed.), Elsevier/North Holland, New York, NY, p. 287.

Levinskas, G. 1981. "A review and evaluation of carcinogenicity studies in mice and rats and mutagenicity studies with polychlorinated biphenyls." Monsanto publications.

Loury, D.J. and J.L. Byard. 1983. Aroclor 1254 pretreatment enhances the DNA repair response to amino acid pyrolysate mutagens in primary cultures of rat hepatocytes. Cancer Lett. 20:283.

Lu, Y.C. and P.N. Wong. 1984. Dermatological, medical, and laboratory findings of patients in Taiwan and their treatments. Am. J. Ind. Med. 5:81.

Makiura, S. et al. 1974. Inhibitory effect polychlorinated biphenyls on liver tumorigenesis in rats treated with 3'-methyl-4-dimethylaminoazobenezene, N-2-fluorenylacetamide and diethylnitrosamine. J. Natl. Cancer Instit. 53:1253.

Masuda, Y. et al. 1982. Comparison of causal agents in Taiwan and Fukuoda PCB poisonings. Chemosphere 11:199.

Masuda, Y. and H. Yoshimura. 1984. Polychlorinated biphenyls and dibenzofurans in patients with Yusho and their toxicological significance. Am. J. Ind. Med. 5:31.

Masuda, Y. et al. 1985. PCB and PCDF congeners in the blood and tissues of Yusho and Yu-Cheng patients. Environ. Health Persp. 59:53.

Miyata, H. et al. 1985. PCBs, PCQs and PCDFs in tissues of Yusho and Yu-Cheng patients. Environ. Health Perspect. 59:67.

Morgan, R.W. et al. 1981. Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats. Cancer Res. 41:5052.

Nagasaki, H. et al. 1972. Hepatocarcinogenicity of polychlorinated biphenyls in mice. Gann 63:805.

NCI (National Cancer Institute). 1978. Bioassay of Aroclor 1254 for Possible Carcinogenicity. DHEW publication No. (NIH) 78-830.

Nishizumi, M. 1980. Reduction of diethylnitrosamine-induced hepatoma in rats exposed to polychlorinated biphenyls through their dams. Gann 71:910.

Nishizumi, M. 1976. Enhancement of diethylnitrosamine

hepatocarcinogenesis in rats by exposure to polychlorinated biphenyls or phenobarbital. Cancer Lett. 2:11.

Norback, D.E. and R.E. Weltman. 1985. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ. Health Persp. 60:97.

Okumura, M. 1984. Past and current medical states of Yusho patients. In: Progress in Clinical and Biological Research, Vol. 137, Alan R. Liss, Inc., New York.

Osterle, D. and E. Deml. 1984. Dose-dependent promoting effect of polychlorinated biphenyls on enzyme-altered islands in liver of adult and weanling rats. Carcinogenesis 5:351.

Pereira, M.A. et al. 1982. Promotion by polychlorinated biphenyls of enzyme-altered foci in rat liver. Cancer Lett. 15:185.

Preston, B.D. et al. 1981. Promoting effects of polychlorinated biphenyls (Aroclor 1254) and dibenzofuran-free Aroclor 1254 on diethylnitrosoamine-induced tumorigenesis in the rat. J. Natl. Cancer Instit. 66:509.

Schaeffer, E. et al. 1984. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol. Appl. Pharmacol. 75:278.

Stott, W.T. and R.O. Sinnuber. 1978. Trout hepatic enzyme activation of aflatoxin B1 in a mutagen assay system and the inhibitory effect of PCBs. Bull. Environ. Contam. Toxicol. 19:35.

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

Warshaw, R. et al. 1979. Decrease in vital capacity in PCB-exposed workers in a capacitor manufacturing facility. N.Y. Acad. Sci. 320:277.

Wolff, M.S. 1982. Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. Int. Arch. Occup. Environ. Health. 49:199.

Young, S.S. 1985. Letter to the Editor. Toxicol. Appl. Pharmacol. 78:321.