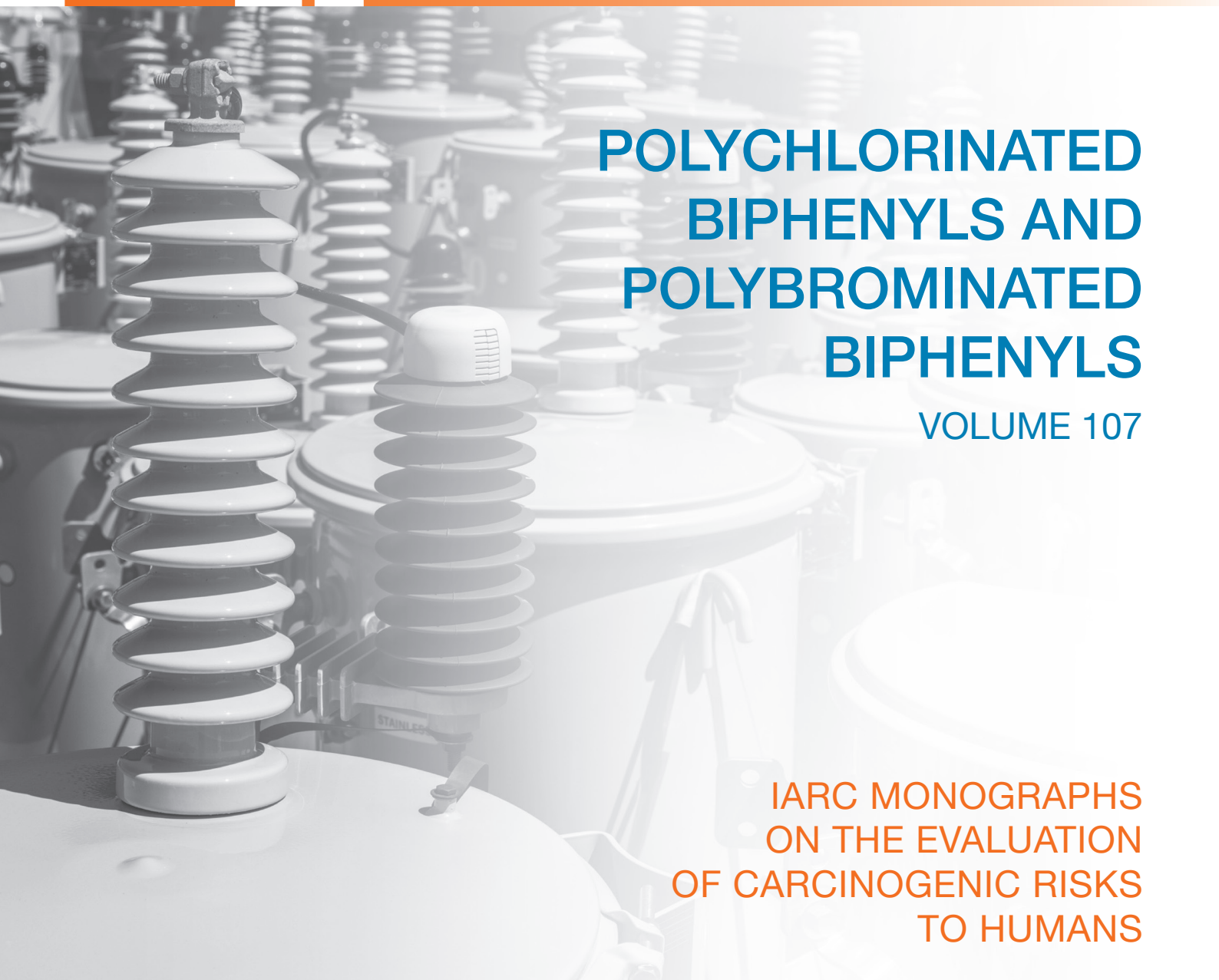
IARC MONOGRAPHS



POLYCHLORINATED BIPHENYLS AND POLYBROMINATED BIPHENYLS

VOLUME 107

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

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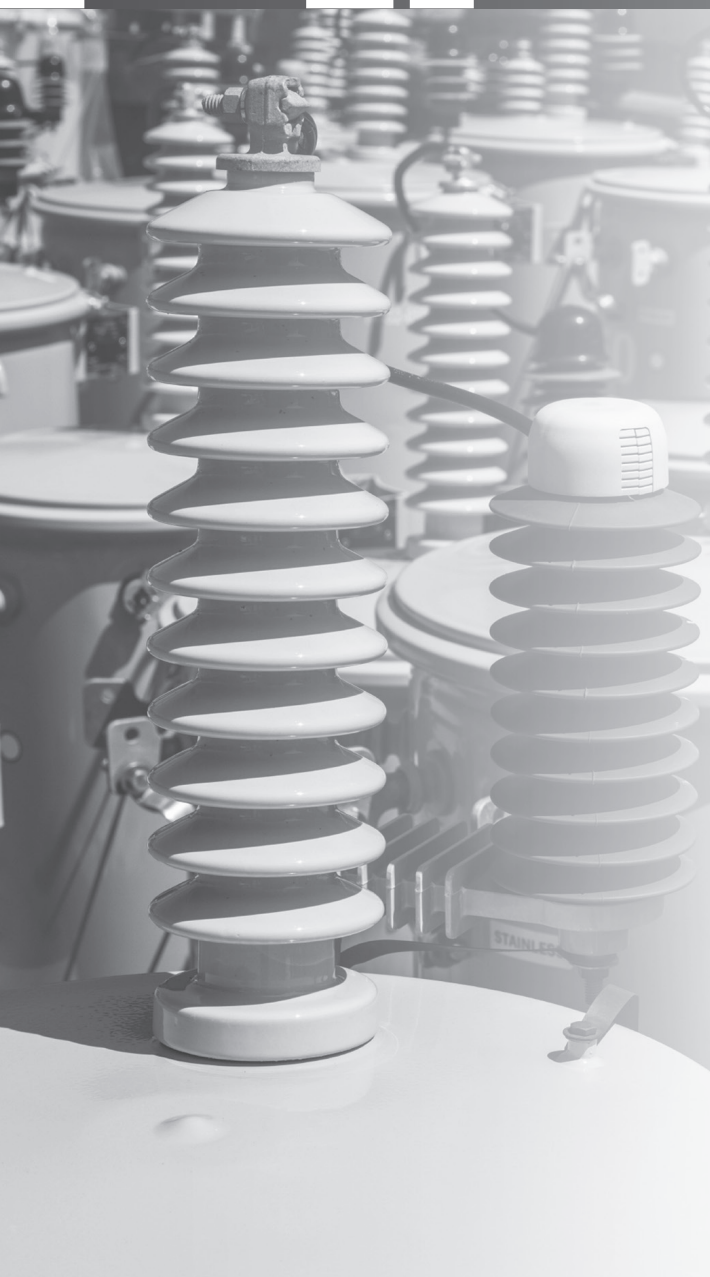
IARC MONOGRAPHS



POLYCHLORINATED BIPHENYLS AND POLYBROMINATED BIPHENYLS

VOLUME 107

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 12–19 February 2013

Lyon, France - 2016

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (2014–2020) (for further information please consult: http://ec.europa.eu/social/easi). Support has also been provided since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

On-line publication, 29 June 2015 (see Corrigenda)

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

Corrigenda to the IARC Monographs are published online at http://monographs.iarc.fr/ENG/Publications/corrigenda.php
To report an error, please contact: editimo@iarc.fr

Co-funded by the European Union

IARC Library Cataloguing in Publication Data

Polychlorinated biphenyls and polybrominated biphenyls / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2013: Lyon, France)

(IARC monographs on the evaluation of carcinogenic risks to humans ; volume 107)

1. Polychlorinated Biphenyls – adverse effects 2. Polychlorinated Biphenyls – metabolism 3. Polychlorinated Biphenyls – toxicity 4. Polybrominated Biphenyls – adverse effects 5. Polybrominated Biphenyls – metabolism
6. Polybrominated Biphenyls – toxicity 7. Carcinogens 8. Neoplasms – chemically induced
I. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans
II. Series

ISBN 978 92 832 4529 2 (NLM Classification: W1)
ISSN 1017-1606

CONTENTS

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US $1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[3] Bernard W. Stewart attended as a Representative of Cancer Australia.
[4] Each Observer agreed to respect the Guidelines for Observers at IARC Monographs meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft any part of a Monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.
[5] Erik Carlson is employed by General Electric Company as a toxicologist and works on PCB-related issues. He has provided expert opinion and testimony in the context of regulatory and legislative process and he holds stocks and bonds from stakeholders.
[6] John Schell has consulted for several companies on PCB-related issues and provided expert opinions on regulatory issues related to PCBs.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate

or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data
Studies of cancer in humans
Studies of cancer in experimental animals
Mechanistic and other relevant data
Summary
Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are

obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population

to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for

confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they

allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in

an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo

transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls,

particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and

the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:** A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:** There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In

addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics,

physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

This one-hundred-and-seventh volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of exposure to polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). The *IARC Monographs* programme has conducted several evaluations of the carcinogenicity of these agents (IARC, 1978, 1979, 1987; Table 1). At the meeting of the Advisory Group to Recommend Priorities for the IARC Monographs in 2008, PCBs were identified as an agent with high priority for re-evaluation (IARC, 2009). In the framework of the re-evaluation of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) in October 2009 (IARC, 2012), the congener PCB-126 was upgraded to Group 1, and the Working Group recommended that there be an in-depth re-evaluation of agents with properties similar to TCDD (IARC, 2012). In February 2013, the *IARC Monographs* Working Group undertook a re-evaluation of PCBs and PBBs. A summary of the findings of this meeting appears in *The Lancet Oncology* (Lauby-Secretan *et al.*, 2013).

1. Considerations for definitions and nomenclature of PCBs and PBBs

Four decades after national governments began to ban their production and use, PCBs and PBBs remain a major concern to human health and the natural environment. Epidemiological studies in occupational settings generally studied workers exposed to the "fresh" product, by inhalation or dermal contact, while studies in the general population assessed individuals exposed primarily through intake of contaminated food, for which the exposure profile is difficult to assess. In contrast, experimental studies assessed individual congeners, combinations of a few congeners, or "fresh" commercial PCB products; however, none of these are identical to the PCB or PBB profiles to which people are exposed today. Indeed, most human exposure today is to complex mixtures originating from commercial products that have been altered by environmental processes (i.e. weathering, transport, and bioaccumulation).

The reason that PCB and PBB mixtures in the environment today differ from the original commercial products is that after release into the environment, the congener composition changes through partitioning, chemical transformation, and bioaccumulation. Partitioning refers to processes by which different congeners separate into air, water, sediment, and soil. Some congeners tend to volatilize or disperse as aerosols, providing an effective vehicle for long-range transport. Congeners with low chlorine or bromine content tend to be more volatile, and also somewhat soluble in water. Many congeners adsorb to organic materials in sediments and

Table 1 Historical overview of the *IARC Monographs* evaluations of PCBs and PBBs

Agent	Volume	Reference	Evidence in humans	Evidence in experimental animals	Mechanistic considerations	Group
PCBs	7	IARC (1974)	No formal evaluation	No formal evaluation	–	–
	18	IARC (1978)	No formal evaluation	No formal evaluation	–	–
	Suppl. 1	IARC (1979)	Inadequate	Sufficient	–	2B[a]
	Suppl. 4	IARC (1982)	Inadequate	Sufficient	–	2B
	Suppl. 7	IARC (1987)	Limited	Sufficient	–	2A
PCB-126	100F	IARC (2012)	–	Sufficient	Mechanistic upgrade	1
PBBs	18	IARC (1978)	No formal evaluation	No formal evaluation	–	
	41	IARC (1986)	Inadequate	Sufficient	No evidence for genotoxicity	–
	Suppl. 7	IARC (1987)	Inadequate	Sufficient	No evidence for genotoxicity	2B

[a] Possible target organs in humans identified as "skin (melanoma)" and "all sites"
PBB, polybrominated biphenyl; PCB, polychlorinated biphenyl

soils; adsorption tends to increase with chlorine or bromine content of the congener and with the organic content of the other material. Chemical transformation refers to the dechlorination or debromination of congeners. This can occur through photolysis, especially for some PBB congeners, or through interactions with bacteria. Chemical transformation is not synonymous with detoxication, as congeners having carcinogenic activity can be formed through dechlorination. Bioaccumulation occurs because PCBs and PBBs are absorbed by fish and other animals, and are highly soluble in lipids, while metabolism and elimination are relatively slower than absorption. Bioaccumulation through the food-chain tends to concentrate congeners of higher chlorine and bromine content.

The nomenclature of PCBs is complex. Publications often attempt to find dichotomies in these mixtures, or refer to PCBs in loose terms, such as:

- Higher and lower chlorinated
- Non-*ortho*, di-*ortho*, and similar terms
- Planar and non-planar
- Dioxin-like and non-dioxin-like
- Aryl hydrocarbon receptor-activating and non-activating
- High and low toxic equivalency (TEQ)
- Estrogenic and non-estrogenic
- Immunotoxic and non-immunotoxic.

The Working Group considered how to characterize the agents to be evaluated. The possibilities included:

- Specific congeners (e.g. PCB-126, PBB-153);
- Groupings of a small number of congeners (e.g. PCB-126 plus PCB-153);
- Commercial products (e.g. Aroclor 1242, Firemaster FF1);
- Large subsets of congeners (e.g. dioxin-like PCB congeners);
- PCBs or PBBs as a class.

Since human exposure always occurs to mixtures, the Working Group considered that it was appropriate to evaluate PCBs and PBBs each as a group.

2. Analysis of PCBs and PBBs

There are some difficulties in assessing and comparing PCB or PBB concentrations in any medium because of differences in analytical methods between laboratories, and differences in the numbers and types of congeners reported. Since there are 209 congeners, values reported

are rarely for true total PCB or PBB concentrations, but rather for a few selected congeners, or a "total" PCB or PBB concentration reported on the basis of analysis of a certain number of congeners only. Thus both the number and the specific congeners analysed must be considered when comparing results among studies. Another complication is that some authors present results for concentrations in total serum (usually called "wet weight"), while others report concentration in the lipid fraction of serum or other media (called "lipid adjusted"). The rationale for lipid adjustment is that these compounds are lipophilic, although there is some evidence that lipid adjustment poses risk of bias. Some investigators now report results as wet weight concentrations with serum lipids considered as a covariate. A further complication is that concentrations are reported in different units in different studies, and cannot always be directly compared.

Several biomarkers of exposure have been used as indicators of the internal dose or the body burden of PCBs or PBBs. These include measurement in blood (serum or plasma), adipose tissue, maternal or cord blood, breast milk and hair. In principle, blood lipid concentrations reflect recent exposures and the full spectrum of congeners to which a person is exposed, while the profile in adipose tissue reflects long-term intakes. However, recent exposure to less chlorinated congeners could result in higher non-equilibrium levels in the circulation. Levels in breast milk largely reflect the concentrations in adipose tissue.

A common theme with PCBs and PBBs is that major industrial accidents have resulted in unforeseeable human dietary exposure. In the 1968 Yusho incident in Japan, leaking Kanechlor 400 contaminated rice oil destined for human consumption. The 1979 Yucheng incident in Taiwan, China, also involved contamination of rice oil, this time by Kanechlor 500. And during 1973–1974, PBBs were unintentionally shipped as an animal feed supplement, contaminating milk, eggs, other dairy products, beef, pork, sheep, and chickens in Michigan, USA. Each incident involved relatively small amounts of PCBs or PBBs, but soon affected thousands of people. It should be noted that the effects of these incidents are not limited to cancer. The Yusho and Yucheng incidents also involved major effects on skin, such as severe chloracne, and recent studies have linked PBB exposure in Michigan to increased risks of spontaneous abortion, genitourinary conditions in male offspring, and suggestions of altered ovarian function.

3. Assessment of exposure to PCBs in epidemiological studies

Epidemiological studies investigating the potential carcinogenic effects of PCBs are basically of three types: occupational cohorts, environmental cohorts, and case–control studies. Most cohort studies were unable to quantify PCB exposures, although in some studies potential PCB exposure was estimated, or a qualitative scale was used. Within some cohort studies, more detailed analyses were achieved through nested case–control studies that collected additional information, sometimes including biomarkers, for specific subgroups of cancer cases and controls. Studies (nested case–control, and case–control) with biomarkers of exposure allow quantification of PCBs in serum or adipose tissue.

In this last group of studies, PCB exposure has been evaluated in a variety of ways: as to a group of congeners; as more or less specific commercial products; as specific PCB functional groupings; as specific combinations, such as PCB-118 + PCB-126; or as specific congeners.

There are several challenges in the interpretation and evaluation of the evidence for PCBs and cancer:

- In studies of workers and consumers of food items allegedly or known to have been "contaminated" with PCBs, it is usually not possible to determine the actual level of exposure.
- PCB exposure usually occurs to mixtures, and while these are often analysed as individual congeners in studies using biomarkers, many congeners are highly correlated and disentangling results for specific congeners is difficult.
- Several specific congeners are rarely or never included in epidemiological studies, primarily because they are excluded from "batch" gas chromatography analyses in many laboratories. Different studies focus on different PCBs; sometimes congeners are grouped and these groupings may differ across studies. Analytical results for specific congeners are best interpreted as markers for exposure to PCBs in general.
- In the occupational cohorts, the exposure route is usually dermal and inhalation, while in the environmental cohorts and case–control studies, the exposure route is usually ingestion (PCB exposure through diet).
- A few environmental studies refer to acute exposures (accidents), while most studies refer to long-term exposures (occupational exposure, and contamination of diet) and long-term consequences of accidents.
- Latency considerations are usually not possible when using biomarker samples collected long after exposure. This may be a cause for concern in interpreting findings on less persistent lower-chlorinated PCBs, but it would be less so for the persistent highly chlorinated PCBs.
- In principle, the use of biomarkers should reduce exposure-measurement error; studies evaluating biomarkers for many PCB congeners tend to generate multiple comparisons, potentially increasing the number of false-positive associations.
- Sampling may be problematic when adjusting plasma or serum measurements by lipid content, because of lipid degradation in samples. Most cohort studies could not take into account relevant confounders, while some of these were considered in the nested case–control and case–control studies.
- Very few studies have addressed interaction or effect modification with other environmental exposures such as tobacco smoke and other chemicals.

4. Genotoxicity of PCBs

Many early tests for genotoxicity with PCBs, performed 10 years ago or more, reported negative results. However, almost all of these studies are not suited for hazard assessment, primarily due to the low doses tested and, in case of studies in vitro, the lack of an exogenous metabolic system. If retested with metabolic activation, many PCB congeners would show genotoxicity. Most PCB mixtures and the few congeners that were tested gave negative results in the Ames test with and without metabolic activation [reviewed in (Silberhorn *et al.*, 1990; Ludewig, 2001)]. A negative result in the Ames test is not uncommon for compounds with complicated and multistep activation pathways such as that proposed for less chlorinated PCBs, i.e. metabolic activation to quinones. Thus a bacterial test for mutagenicity is probably not an appropriate assay for evaluating the genotoxicity of PCBs.

5. The pleiotropic carcinogenicity of PCBs

In experimental animals, commercial PCB mixtures and some individual congeners are complete carcinogens, producing neoplastic

lesions primarily in the liver (hepatocytes and biliary tract); however, benign and malignant tumours have also been observed in many other organs of the treated animals (lung, oral mucosa, thyroid gland, uterus, skin, and the mammary gland in the offspring of treated mothers).

Accidental release of PCBs into food in Taiwan, China, and in Japan, has led to acute and chronic PCB toxicity in thousands of people. Examination of the mortality rate of the Yusho victims in Japan 40 years after the event revealed an increased risk of all types of cancer combined, cancers of the liver and lung in men, and cancer of the liver in women (Onozuka *et al.*, 2009). A similar 24-year follow-up study of Yucheng victims in Taiwan, China, found increased mortality from liver disease, but no increase in risk of cancer of the liver (Tsai *et al.*, 2007). After reviewing all epidemiological studies on occupational and environmental exposure to PCBs, the Working Group concluded that there was *sufficient evidence* of carcinogenicity in humans, on the basis of an increased risk of malignant melanoma; one study found a significant association with uveal melanoma in exposed workers. In addition, increased risks were seen in some studies between exposure to PCBs and non-Hodgkin lymphoma, and for cancer of the breast in some subgroups of women. Positive findings were observed in individual studies for cancers of the brain, prostate, stomach, and pancreas.

PCBs bioaccumulate in fatty tissue, so higher marine mammals are particularly exposed. Reports of cancers in marine wildlife living in areas with high measured PCB concentrations provide another source of cancer data. For example, a large cell immunoblastic lymphoma in a bottlenose dolphin (*Tursiops truncates*) with high blood PCB concentrations (Jaber *et al.*, 2005); uterine leiomyomas in 257 female Baltic grey seals (*Halichoerus grypus*) (Bredhult *et al.*, 2008); and undefined carcinomas in 38 stranded wild California sea lions (*Zalophus californianus*), which were reported to be strongly associated with high PCB concentrations measured in the animals (Ylitalo *et al.*, 2005).

6. Toxicity and carcinogenicity of PBBs

The Working Group also considered the evidence on carcinogenicity of PBBs. The chemical structure of PBBs resembles that of PCBs, with substitution by bromine rather than chlorine atoms. PBBs were used primarily as flame retardants in the 1970s, but production has been discontinued in most countries for many years. Following the accidental release of PBBs in Michigan, USA, the one study that investigated cancer reported adjusted odds ratios of up to 23-fold for cancer of the digestive system and up to 33-fold for lymphoma, with an exposure–response trend across exposure groups. This study included cancer results until 1993; the study has not yet been updated to include cancers that have occurred during the subsequent 20 years. Concerning experimental and mechanistic studies, while there is an extensive body of literature on the carcinogenicity of PCBs, their brominated analogues have received much less attention and study. PBBs will likely be found to exhibit their toxicity and disease potential via many of the same pathways as their chlorinated counterparts, with equivalent or greater toxicity.

The information contained in this volume has contributed to the report "Health risks of PCB in the indoor climate in Denmark," published by the Sundhedsstyrelsen (Danish Health and Medicines Authority, 2013) and was considered during the evaluation of non-dioxin like PCBs by the Joint FAO/WHO Expert Committee on Food Additives (June 2015).

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POLYCHLORINATED BIPHENYLS

1. EXPOSURE DATA

1.1 Identification of the agent

1.1.1 Nomenclature

Polychlorinated biphenyls (PCBs) are a class of aromatic chemical compounds in which some or all hydrogen atoms attached to the biphenyl ring are substituted by chlorine atoms (m + n = 1–10) (Fig. 1.1). Synonyms for PCBs include chlorinated biphenyls, chlorinated diphenyls, chlorobiphenyls, or polychlorobiphenyls.

The general chemical formula is $C_{12}H_{(10-m-n)}Cl_{(m+n)}$, where (m + n) is the number of chlorine atoms on the two rings. Depending on the position and number of the chlorine atoms, there are theoretically 209 individual PCB compounds (congeners). The carbon positions are numbered 1 to 6 on one ring, and 1′ to 6′ on the other. While positions 2,2′,6, and 6′ are called "*ortho*," positions 3,3′,5 and 5′ are named "*meta*" and positions 4 and 4′ are called "*para*."

Two different but correlated nomenclature systems are currently used. According to the International Union of Pure and Applied Chemistry (IUPAC) and in particular rule A-52.3 related to hydrocarbon systems, an unprimed number is considered lower (higher priority) than the same number when primed. Assemblies of unprimed and primed numbers are arranged in ascending numerical order. For a given PCB congener, the name lists the numbers sequentially [e.g. the PCB congener with chlorines on carbons 2,4,5, and 3′,4′ is identified as 2,3′,4,4′,5 (and not 2′,3,4,4′,5′)]. A deviation in that system lists the unprimed and primed chlorinated ring positions separately, sometimes eliminating the prime symbols and the commas for clarity and ease of typing (e.g. 245–3′4′5′ or 245–345).

In an additional strategy proposed by Ballschmiter & Zell (1980), a number (called "BZ number") is attributed to each individual congener. This number correlates the structural arrangement of the PCB congener and ascending order of number of chlorine substitutions within each sequential homologue (Ballschmiter & Zell, 1980). This results in the congeners being numbered from PCB-1 to PCB-209. This shorthand nomenclature has become quite popular and is convenient for many uses, although it is important to note that it obscures the chemical identity of the congener and does not strictly follow the IUPAC rules.

Slight changes in the original BZ congener-numbering system were later recommended to correct some errors (Schulte & Malisch, 1983; Ballschmiter *et al.*, 1992), and this resulted in the renumbering of BZ numbers 199–201. Guitart *et al.* (1993) used a computer program to systematically renumber the PCBs according to the strict IUPAC rules. As a result, they recommended that the congeners previously numbered 107, 108, 109, 199, 200, and 201 be renumbered 109, 107, 108, 200, 201, and 199, respectively (reviewed in Mills *et al.*, 2007). The nomenclature for PCB congeners based on this report is shown in Table 1.1 and will be preferred in this *Monograph*. However, in the scientific literature,

Table 1.1 Correspondance between BZ number[a] and position of chlorine atoms on each phenyl ring of the PCBs[b]

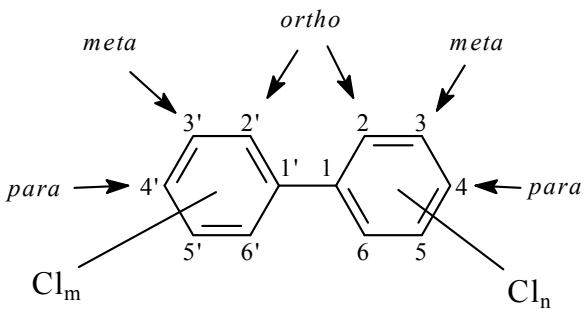
Position of chlorine atom on each ring	2	3	4	2,3	2,4	2,5	2,6	3,4	3,5	2,3,4	2,3,5	2,3,6	2,4,5	2,4,6	3,4,5	2,3,4,5	2,3,4,6	2,3,5,6	2,3,4,5,6
None	1	2	3	5	7	9	10	12	14	21	23	24	29	30	38	61	62	65	116
2′	4	6	8	16	17	18	19	33	34	41	43	45	48	50	76	86	88	93	142
3′		11	13	20	25	26	27	35	36	55	57	59	67	69	78	106	108	112	160
4′			15	22	28	31	32	37	39	60	63	64	74	75	**81**	**114**	115	117	166
2′,3′				40	42	44	46	56	58	82	83	84	97	98	122	129	131	134	173
2′,4′					47	49	51	66	68	85	90	91	99	100	**123**	137	139	147	181
2′,5′						52	53	70	72	87	92	95	101	103	124	141	144	151	185
2′,6′							54	71	73	89	94	96	102	104	125	143	145	152	186
3′,4′								**77**	79	**105**	109	110	**118**	119	**126**	**156**	158	163	190
3′,5′									80	107	111	113	120	121	127	159	161	165	192
2′,3′,4′										128	130	132	138	140	**157**	170	171	177	195
2′,3′,5′											133	135	146	148	162	172	175	178	198
2′,3′,6′												136	149	150	164	174	176	179	200
2′,4′,5′													153	154	**167**	180	183	187	203
2′,4′,6′														155	168	182	184	188	204
3′,4′,5′															**169**	**189**	191	193	205
2′,3′,4′,5′																194	196	199	206
2′,3′,4′,6′																	197	201	207
2′,3′,5′,6′																		202	208
2′,3′,4′,5′,6′																			209

[a] Revised PCB numbering system, including the revised numbering of congeners 107–109 and 199–201. For several PCB congeners, the indicated (truncated) structural names do not strictly adhere to the IUPAC rules (primed and unprimed numbers are interchanged). A comprehensive review of PCB nomenclature, including IUPAC names, is given in Mills *et al.* (2007).

[b] Dioxin-like PCBs are indicated in bold type

BZ, Ballschmiter and Zell; IUPAC, International Union of Pure and Applied Chemistry; PCB, polychlorinated biphenyl

Fig. 1.1 Chemical structure of PCBs and the IUPAC numbering system



Hydrogen atoms in positions 2,2′,6,6′ (*ortho*), 3,3′,5,5′ (*meta*) and/or 4,4′ (*para*) may be substituted by chlorine atoms; (m + n) is the number of chlorine atoms on the two rings
IUPAC, International Union of Pure and Applied Chemistry; PCB, polychlorinated biphenyl

the revised numbering of congeners 107–109 has not been adopted systematically; the numbering system commonly used has been that proposed by Ballschmiter *et al.* (1992) where only the original BZ numbers 199–201 are changed.

PCBs can be categorized by degree of chlorination (number of chlorine atoms) in 10 homologue groups (Table 1.2) from monochlorobiphenyls to decachlorobiphenyls. More than 60% of the PCBs are tetra- to hexachlorophenyls.

In the biphenyl molecule, the two aromatic rings can rotate about the connecting single 1,1′-bond (Fig. 1.1). As with all molecules, there is a low-energy preferred conformation. With PCBs, this conformation is dependent on the degree of chlorine substitution, since chlorine is larger than hydrogen and creates more steric hindrance to the rotation (Erickson, 2001). The two extreme theoretical configurations are "planar" or "coplanar," in which the two benzene rings are in the same plane, and "non-planar" in which the benzene rings are at a 90° angle to each other (Faroon *et al.*, 2000). The probability of attaining a planar configuration is essentially determined by the number of substitutions in the *ortho* positions (2,2′,6,6′): the benzene rings of non-*ortho* substituted PCBs as well as mono-*ortho* substituted PCBs can assume a planar configuration and are referred to as "planar" or "coplanar" congeners (Erickson, 1997). The replacement of hydrogen atoms in the *ortho* positions with larger chlorine atoms forces the aromatic rings to rotate out of the planar configuration (Fig. 1.2); such structures are referred to as "non-planar" or "non-coplanar" congeners. [The Working Group does not recommend the use of this terminology, which is not technically appropriate since these PCBs do not easily assume a planar conformation.]

The relationship between PCB congener number and the Chemical Abstracts Service (CAS) registry number is given in Table 1.3. The congener numbering presented in this table follows that in Table 1.1, with the revised numbering of congeners 107–109. The congener lipophilicity is given in the same table, and was expressed against capacity to partition in octanol and water (K_{ow}) (see Section 1.1.2). Congeners can also be characterized by descriptors (CP0, CP1, 4Cl, PP, 2M) that give rapid access to geometry and substituent positions. The first descriptor, CP0, characterizes 20 congeners that are referred to as non-*ortho* congeners, consisting of those with chlorine substitution at none of the *ortho* positions on the biphenyl backbone. The second descriptor, CP1, comprises 48 congeners that are referred to as mono-*ortho* congeners and include those with chlorine substitution at only one of the *ortho* positions; CP0 and CP1 congeners can adopt a planar configuration. The 4Cl descriptor designates 169 congeners that have a total of four or more chlorine substituents, regardless of position. There are 54 PP congeners that have both *para* positions chlorinated. The 2M group contains 140 congeners that have two or more of the *meta* positions chlorinated. A total of 11 congeners have no descriptor.

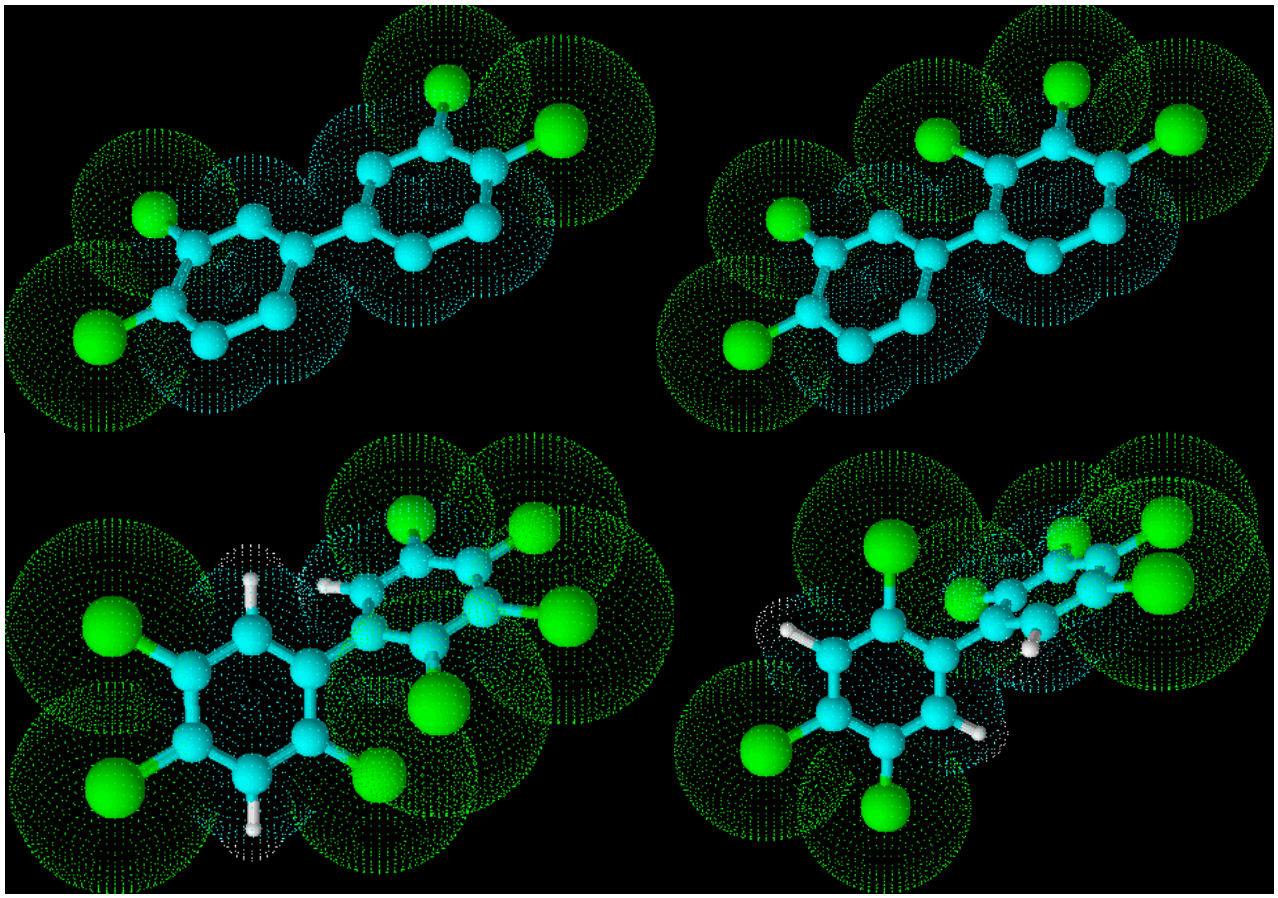
The twelve congeners that display all descriptors are referred to as "dioxin-like" (Table 1.4). These twelve PCBs, namely PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-156, PCB-157, PCB-167, PCB-169, and

Table 1.2 Physical and chemical properties of PCBs according to homologue group

Homologue group	CAS No.	Formula	No. of isomers	BZ No.	Relative molecular mass	Chlorine (% w/w)	Vapour pressure (Pa at 25 °C)[a]	Melting point (°C)[b]	Boiling point (°C)[c]
Monochlorobiphenyl	27323-18-8	$C_{12}H_9Cl$	3	1–3	188.66	18.79	1.1	25–77.9	285
Dichlorobiphenyl	25512-42-9	$C_{12}H_8Cl_2$	12	4–15	223.10	31.77	0.24	24.4–149	312
Trichlorobiphenyl	25323-68-6	$C_{12}H_7Cl_3$	24	16–39	257.55	41.30	0.054	28–87	337
Tetrachlorobiphenyl	26914-33-0	$C_{12}H_6Cl_4$	42	40–81	291.99	48.65	0.012	47–180	360
Pentachlorobiphenyl	25429-29-2	$C_{12}H_5Cl_5$	46	82–127	326.44	54.30	$2.6.10^{-3}$	76.5–124	381
Hexachlorobiphenyl	26601-64-9	$C_{12}H_4Cl_6$	42	128–169	360.88	58.93	$5.8.10^{-4}$	77–200	400
Heptachlorobiphenyl	28655-71-2	$C_{12}H_3Cl_7$	24	170–193	395.33	62.77	$1.3.10^{-4}$	83–149	417
Octachlorobiphenyl	55722-26-4	$C_{12}H_2Cl_8$	12	194–205	429.77	65.98	$2.8.10^{-5}$	159–162	432
Nonachlorobiphenyl	53742-07-7	$C_{12}HCl_9$	3	206–208	464.22	68.73	$6.3.10^{-6}$	182.8–206	445
Decachlorobiphenyl	2051-24-3	$C_{12}Cl_{10}$	1	209	498.66	71.10	$1.4.10^{-6}$	305.9	456

[a] Mean value for liquid.
[b] Values are approximations of the range across the isomers.
[c] Average value of all isomers in the group.
[The Working Group noted that the CAS No. for octachlorobiphenyl homologue group differs between ATSDR (2000) and Lindell (2012).]
BZ, Ballschmiter and Zell; CAS, Chemical Abstracts Service
From Shiu & Mackay (1986), ATSDR (2000), Erickson (2001), and Lindell (2012)

Fig. 1.2 Tridimensional chemical structures of selected PCBs



Upper panel: Spatial configuration of two dioxin-like PCBs: PCB-77 (3,3′,4,4′-tetrachlorobiphenyl), a non-*ortho* congener (left), and PCB-105 (2,3,3′,4,4′-pentachlorobiphenyl), a mono-*ortho* congener (right)
Lower panel: Spatial configuration of two di-*ortho* PCBs: PCB-153 (2,2′,4,4′,5,5′-hexachlorobiphenyl; left) and PCB-180 (2,2′,3,4,4′,5,5′-heptachlorobiphenyl; right)
Courtesy of Professor B. LeBizec

PCB-189, have been assigned toxicity equivalency factors (TEFs, assigned by WHO in 1998 and revised in 2005) (Van den Berg *et al.*, 2006). [The Working Group stressed that the activities of these PCB congeners are not solely dioxin-like.]

Depending on the context of the study or investigation, specific congeners may be monitored. For instance, the Stockholm Convention on Persistent Organic Pollutants (POPS) recommends measurement of six indicator PCBs (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, and PCB-180) to characterize contamination by PCBs. These congeners were chosen because they are found at higher concentrations in the environment, in food, or in human fluids/tissues. Depending on country and context, different lists of varying numbers of congeners may be used, e.g. 36 congeners for the Centers for Disease Control and Prevention, USA, or only PCB-138, PCB-153, and PCB-180 most frequently in epidemiological studies with human blood (see Section 2).

Of the 209 PCB congeners, 78 display axial chirality. Only 19 of these congeners, those with three or more chlorine atoms in the *ortho* position, exist as two mirror-image atropisomers, i.e. two chiral atropisomers (Lehmler & Robertson,

Table 1.3 Relationship between BZ number, CAS number, IUPAC name,[a] congener descriptor, and log K_{ow} for individual PCBs

BZ No.	IUPAC name	CAS No.	Descriptor[b]	Log K_{ow}	Vapour pressure (atm at 25 °C)[c]
1	2-CB	2051-60-7	CP1	4.46	
2	3-CB	2051-61-8	CP0	4.69	
3	4-CB	2051-62-9	CP0	4.69	
4	2,2′-DiCB	13029-08-8		4.65	1.5 to 4.2×10^{-6}
5	2,3-DiCB	16605-91-7	CP1	4.97	
6	2,3′-DiCB	25569-80-6	CP1	5.06	
7	2,4-DiCB	33284-50-3	CP1	5.07	9.9×10^{-7} to 2.1×10^{-6}
8	2,4′-DiCB	34883-43-7	CP1	5.07	
9	2,5-DiCB	34883-39-1	CP1	5.06	2.0 to 2.3×10^{-6}
10	2,6-DiCB	33146-45-1		4.84	
11	3,3′-DiCB	2050-67-1	CP0, 2M	5.28	4.1 to 9.1×10^{-7}
12	3,4-DiCB	2974-92-7	CP0	5.22	1.3×10^{-8} to 7.8×10^{-7}
13	3,4′-DiCB	2974-90-5	CP0	5.29	
14	3,5-DiCB	34883-41-5	CP0, 2M	5.28	
15	4,4′-DiCB	2050-68-2	CP0, PP	5.30	5.0 to 7.4×10^{-7}
16	2,2′,3-TriCB	38444-78-9		5.16	
17	2,2′,4-TriCB	37680-66-3		5.25	
18	2,2′,5-TriCB	37680-65-2		5.24	3.5×10^{-7} to 1.2×10^{-6}
19	2,2′,6-TriCB	38444-73-4		5.02	
20	2,3,3′-TriCB	38444-84-7	CP1, 2M	5.57	
21	2,3,4-TriCB	55702-46-0	CP1	5.51	
22	2,3,4′-TriCB	38444-85-8	CP1	5.58	
23	2,3,5-TriCB	55720-44-0	CP1, 2M	5.57	
24	2,3,6-TriCB	55702-45-9		5.35	
25	2,3′,4-TriCB	55712-37-3	CP1	5.67	
26	2,3′,5-TriCB	38444-81-4	CP1, 2M	5.66	1.8 to 4.5×10^{-7}
27	2,3′,6-TriCB	38444-76-7		5.44	
28	2,4,4′-TriCB	7012-37-5	CP1, PP	5.67	1.5 to 3.3×10^{-7}
29	2,4,5-TriCB	15862-07-4	CP1	5.60	
30	2,4,6-TriCB	35693-92-6		5.44	9.3×10^{-7} to 1.5×10^{-6}
31	2,4′,5-TriCB	16606-02-3	CP1	5.67	
32	2,4′,6-TriCB	38444-77-8		5.44	
33	2,3′,4′-TriCB	38444-86-9	CP1	5.60	
34	2,3′,5′-TriCB	37680-68-5	CP1, 2M	5.66	
35	3,3′,4-TriCB	37680-69-6	CP0, 2M	5.82	
36	3,3′,5-TriCB	38444-87-0	CP0, 2M	5.88	
37	3,4,4′-TriCB	38444-90-5	CP0, PP	5.83	
38	3,4,5-TriCB	53555-66-1	CP0, 2M	5.76	
39	3,4′,5-TriCB	38444-88-1	CP0, 2M	5.89	
40	2,2′,3,3′-TetraCB	38444-93-8	4CL, 2M	5.66	4.5×10^{-8} to 1.1×10^{-7}
41	2,2′,3,4-TetraCB	52663-59-9	4CL	5.69	
42	2,2′,3,4′-TetraCB	36559-22-5	4CL	5.76	
43	2,2′,3,5-TetraCB	70362-46-8	4CL, 2M	5.75	
44	2,2′,3,5′-TetraCB	41464-39-5	4CL, 2M	5.75	

Table 1.3 (continued)

BZ No.	IUPAC name	CAS No.	Descriptor[b]	Log K_{ow}	Vapour pressure (atm at 25 °C)[c]
45	2,2′,3,6-TetraCB	70362-45-7	4CL	5.53	
46	2,2′,3,6′-TetraCB	41464-47-5	4CL	5.53	
47	2,2′,4,4′-TetraCB	2437-79-8	4CL, PP	5.85	
48	2,2′,4,5-TetraCB	70362-47-9	4CL	5.78	
49	2,2′,4,5′-TetraCB	41464-40-8	4CL	5.85	
50	2,2′,4,6-TetraCB	62796-65-0	4CL	5.63	
51	2,2′,4,6′-TetraCB	68194-04-7	4CL	5.63	
52	2,2′,5,5′-TetraCB	35693-99-3	4CL, 2M	5.84	$1.8 \text{ to } 8.9 \times 10^{-7}$
53	2,2′,5,6′-TetraCB	41464-41-9	4CL	5.62	$1.1 \text{ to } 4.0 \times 10^{-7}$
54	2,2′,6,6′-TetraCB	15968-05-5	4CL	5.21	$1.2 \times 10^{-6} \text{ to } 6.5 \times 10^{-7}$
55	2,3,3′,4-TetraCB	74338-24-2	CP1, 4CL, 2M	6.11	
56	2,3,3′,4′-TetraCB	41464-43-1	CP1, 4CL, 2M	6.11	
57	2,3,3′,5-TetraCB	70424-67-8	CP1, 4CL, 2M	6.17	
58	2,3,3′,5′-TetraCB	41464-49-7	CP1, 4CL, 2M	6.17	
59	2,3,3′,6-TetraCB	74472-33-6	4CL, 2M	5.95	
60	2,3,4,4′-TetraCB	33025-41-1	CP1, 4CL, PP	6.11	
61	2,3,4,5-TetraCB	33284-53-6	CP1, 4CL, 2M	6.04	
62	2,3,4,6-TetraCB	54230-22-7	4CL	5.89	
63	2,3,4′,5-TetraCB	74472-34-7	CP1, 4CL, 2M	6.17	
64	2,3,4′,6-TetraCB	52663-58-8	4CL	5.95	
65	2,3,5,6-TetraCB	33284-54-7	4CL, 2M	5.86	
66	2,3′,4,4′-TetraCB	32598-10-0	CP1, 4CL, PP	6.20	
67	2,3′,4,5-TetraCB	73575-53-8	CP1, 4CL, 2M	6.20	
68	2,3′,4,5′-TetraCB	73575-52-7	CP1, 4CL, 2M	6.26	
69	2,3′,4,6-TetraCB	60233-24-1	4CL	6.04	
70	2,3′,4′,5-TetraCB	32598-11-1	CP1, 4CL, 2M	6.20	
71	2,3′,4′,6-TetraCB	41464-46-4	4CL	5.98	
72	2,3′,5,5′-TetraCB	41464-42-0	CP1, 4CL, 2M	6.26	
73	2,3′,5′,6-TetraCB	74338-23-1	4CL, 2M	6.04	
74	2,4,4′,5-TetraCB	32690-93-0	CP1, 4CL, PP	6.20	
75	2,4,4′,6-TetraCB	32598-12-2	4CL, PP	6.05	
76	2,3′,4′,5′-TetraCB	70362-48-0	CP1, 4CL, 2M	6.13	
77	3,3′,4,4′-TetraCB	32598-13-3	**CP0, 4CL, PP, 2M**	6.36	$5.2 \times 10^{-9} \text{ to } 2.1 \times 10^{-8}$
78	3,3′,4,5-TetraCB	70362-49-1	CP0, 4CL, 2M	6.35	
79	3,3′,4,5′-TetraCB	41464-48-6	CP0, 4CL, 2M	6.42	
80	3,3′,5,5′-TetraCB	33284-52-5	CP0, 4CL, 2M	6.48	
81	3,4,4′,5-TetraCB	70362-50-4	**CP0, 4CL, PP, 2M**	6.36	
82	2,2′,3,3′,4-PentaCB	52663-62-4	4CL, 2M	6.20	
83	2,2′,3,3′,5-PentaCB	60145-20-2	4CL, 2M	6.26	
84	2,2′,3,3′,6-PentaCB	52663-60-2	4CL, 2M	6.04	
85	2,2′,3,4,4′-PentaCB	65510-45-4	4CL, PP	6.30	
86	2,2′,3,4,5-PentaCB	55312-69-1	4CL, 2M	6.23	
87	2,2′,3,4,5′-PentaCB	38380-02-8	4CL, 2M	6.29	
88	2,2′,3,4,6-PentaCB	55215-17-3	4CL	6.07	
89	2,2′,3,4,6′-PentaCB	73575-57-2	4CL	6.07	

Table 1.3 (continued)

BZ No.	IUPAC name	CAS No.	Descriptor[b]	Log K_{ow}	Vapour pressure (atm at 25 °C)[c]
90	2,2′,3,4′,5-PentaCB	68194-07-0	4CL, 2M	6.36	
91	2,2′,3,4′,6-PentaCB	68194-05-8	4CL	6.13	
92	2,2′,3,5,5′-PentaCB	52663-61-3	4CL, 2M	6.35	
93	2,2′,3,5,6-PentaCB	73575-56-1	4CL, 2M	6.04	
94	2,2′,3,5,6′-PentaCB	73575-55-0	4CL, 2M	6.13	
95	2,2′,3,5′,6-PentaCB	38379-99-6	4CL, 2M	6.13	
96	2,2′,3,6,6′-PentaCB	73575-54-9	4CL	5.71	
97	2,2′,3,4′,5′-PentaCB	41464-51-1	4CL, 2M	6.29	
98	2,2′,3,4′,6′-PentaCB	60233-25-2	4CL	6.13	
99	2,2′,4,4′,5-PentaCB	38380-01-7	4CL, PP	6.39	
100	2,2′,4,4′,6-PentaCB	39485-83-1	4CL, PP	6.23	
101	2,2′,4,5,5′-PentaCB	37680-73-2	4CL, 2M	6.38	$1.4 \text{ to } 3.5 \times 10^{-8}$
102	2,2′,4,5,6′-PentaCB	68194-06-9	4CL	6.16	
103	2,2′,4,5′,6-PentaCB	60145-21-3	4CL	6.22	
104	2,2′,4,6,6′-PentaCB	56558-16-8	4CL	5.81	$4.3 \times 10^{-8} \text{ to } 1.7 \times 10^{-7}$
105	2,3,3′,4,4′-PentaCB	32598-14-4	**CP1, 4CL, PP, 2M**	6.65	8.6×10^{-9}
106	2,3,3′,4,5-PentaCB	70424-69-0	CP1, 4CL, 2M	6.64	
107	2,3,3′,4,5′-PentaCB	70424-68-9	CP1, 4CL, 2M	6.71	
108	2,3,3′,4,6-PentaCB	70362-41-3	4CL, 2M	6.72	
109	2,3,3′,4′,5-PentaCB	74472-35-8	CP1, 4CL, 2M	6.48	
110	2,3,3′,4′,6-PentaCB	38380-03-9	4CL, 2M	6.48	
111	2,3,3′,5,5′-PentaCB	39635-32-0	CP1, 4CL, 2M	6.76	
112	2,3,3′,5,6-PentaCB	74472-36-9	4CL, 2M	6.45	
113	2,3,3′,5′,6-PentaCB	68194-10-5	4CL, 2M	6.54	
114	2,3,4,4′,5-PentaCB	74472-37-0	**CP1, 4CL, PP, 2M**	6.65	
115	2,3,4,4′,6-PentaCB	74472-38-1	4CL, PP	6.49	
116	2,3,4,5,6-PentaCB	18259-05-7	4CL, 2M	6.33	
117	2,3,4′,5,6-PentaCB	68194-11-6	4CL, 2M	6.46	
118	2,3′,4,4′,5-PentaCB	31508-00-6	**CP1, 4CL, PP, 2M**	6.74	1.2×10^{-8}
119	2,3′,4,4′,6-PentaCB	56558-17-9	4CL, PP	6.58	
120	2,3′,4,5,5′-PentaCB	68194-12-7	CP1, 4CL, 2M	6.79	
121	2,3′,4,5′,6-PentaCB	56558-18-0	4CL, 2M	6.64	
122	2,3,3′,4′,5′-PentaCB	76842-07-4	CP1, 4CL, 2M	6.64	
123	2,3′,4,4′,5′-PentaCB	65510-44-3	**CP1, 4CL, PP, 2M**	6.74	
124	2,3′,4′,5,5′-PentaCB	70424-70-3	CP1, 4CL, 2M	6.73	
125	2,3′,4′,5′,6-PentaCB	74472-39-2	4CL, 2M	6.51	
126	3,3′,4,4′,5-PentaCB	57465-28-8	**CP0, 4CL, PP, 2M**	6.89	
127	3,3′,4,5,5′-PentaCB	39635-33-1	CP0, 4CL, 2M	6.95	
128	2,2′,3,3′,4,4′-HexaCB	38380-07-3	4CL, PP, 2M	6.74	$1.0 \text{ to } 3.6 \times 10^{-9}$
129	2,2′,3,3′,4,5-HexaCB	55215-18-4	4CL, 2M	6.73	
130	2,2′,3,3′,4,5′-HexaCB	52663-66-8	4CL, 2M	6.80	
131	2,2′,3,3′,4,6-HexaCB	61798-70-7	4CL, 2M	6.58	
132	2,2′,3,3′,4,6′-HexaCB	38380-05-1	4CL, 2M	6.58	
133	2,2′,3,3′,5,5′-HexaCB	35694-04-3	4CL, 2M	6.86	
134	2,2′,3,3′,5,6-HexaCB	52704-70-8	4CL, 2M	6.55	

Table 1.3 (continued)

BZ No.	IUPAC name	CAS No.	Descriptor[b]	Log K_{ow}	Vapour pressure (atm at 25 °C)[c]
135	2,2′,3,3′,5,6′-HexaCB	52744-13-5	4CL, 2M	6.64	
136	2,2′,3,3′,6,6′-HexaCB	38411-22-2	4CL, 2M	6.22	
137	2,2′3,4,4′,5-HexaCB	35694-06-5	4CL, PP, 2M	6.83	
138	2,2′,3,4,4′,5′-HexaCB	35065-28-2	4CL, PP, 2M	6.83	5.2×10^{-9}
139	2,2′,3,4,4′,6-HexaCB	56030-56-9	4CL, PP	6.67	
140	2,2′,3,4,4′,6′-HexaCB	59291-64-4	4CL, PP	6.67	
141	2,2′,3,4,5,5′-HexaCB	52712-04-6	4CL, 2M	6.82	
142	2,2′,3,4,5,6-HexaCB	41411-61-4	4CL, 2M	6.51	
143	2,2′,3,4,5,6′-HexaCB	68194-15-0	4CL, 2M	6.60	
144	2,2′,3,4,5′,6-HexaCB	68194-14-9	4CL, 2M	6.67	
145	2,2′,3,4,6,6′-HexaCB	74472-40-5	4CL	6.25	
146	2,2′,3,4′,5,5′-HexaCB	51908-16-8	4CL, 2M	6.89	
147	2,2′,3,4′,5,6-HexaCB	68194-13-8	4CL, 2M	6.64	
148	2,2′,3,4′,5,6′-HexaCB	74472-41-6	4CL, 2M	6.73	
149	2,2′,3,4′,5′,6-HexaCB	38380-04-0	4CL, 2M	6.67	
150	2,2′,3,4′,6,6′-HexaCB	68194-08-1	4CL	6.32	
151	2,2′,3,5,5′,6-HexaCB	52663-63-5	4CL, 2M	6.64	
152	2,2′,3,5,6,6′-HexaCB	68194-09-2	4CL, 2M	6.22	
153	2,2′,4,4′,5,5′-HexaCB	35065-27-1	4CL, PP, 2M	6.92	1.9×10^{-9} to 6.9×10^{-8}
154	2,2′,4,4′,5,6′-HexaCB	60145-22-4	4CL, PP	6.76	
155	2,2′,4,4′,6,6′-HexaCB	33979-03-2	4CL, PP	6.41	3.5×10^{-9} to 4.4×10^{-8}
156	2,3,3′,4,4′,5-HexaCB	38380-08-4	**CP1, 4CL, PP, 2M**	7.18	2.1×10^{-9}
157	2,3,3′,4,4′,5′-HexaCB	69782-90-7	**CP1, 4CL, PP, 2M**	7.18	
158	2,3,3′,4,4′,6-HexaCB	74472-42-7	4CL, PP, 2M	7.02	
159	2,3,3′,4,5,5′-HexaCB	39635-35-3	CP1, 4CL, 2M	7.24	
160	2,3,3′,4,5,6-HexaCB	41411-62-5	4CL, 2M	6.93	
161	2,3,3′,4,5′,6-HexaCB	74472-43-8	4CL, 2M	7.08	
162	2,3,3′,4′,5,5′-HexaCB	39635-34-2	CP1, 4CL, 2M	7.24	
163	2,3,3′,4′,5,6-HexaCB	74472-44-9	4CL, 2M	6.99	7.9×10^{-10}
164	2,3,3′,4′,5′,6-HexaCB	74472-45-0	4CL, 2M	7.02	
165	2,3,3′,5,5′,6-HexaCB	74472-46-1	4CL, 2M	7.05	
166	2,3,4,4′,5,6-HexaCB	41411-63-6	4CL, PP, 2M	6.93	
167	2,3′,4,4′,5,5′-HexaCB	52663-72-6	**CP1, 4CL, PP, 2M**	7.27	
168	2,3′,4,4′,5′,6-HexaCB	59291-65-5	4CL, PP, 2M	7.11	
169	3,3′,4,4′,5,5′-HexaCB	32774-16-6	**CP0, 4CL, PP, 2M**	7.42	7.9×10^{-10}
170	2,2′,3,3′,4,4′,5-HeptaCB	35065-30-6	4CL, PP, 2M	7.27	
171	2,2′,3,3′,4,4′,6-HeptaCB	52663-71-5	4CL, PP, 2M	7.11	
172	2,2′,3,3′,4,5,5′-HeptaCB	52663-74-8	4CL, 2M	7.33	
173	2,2′,3,3′,4,5,6-HeptaCB	68194-16-1	4CL, 2M	7.02	
174	2,2′,3,3′,4,5,6′-HeptaCB	38411-25-5	4CL, 2M	7.11	
175	2,2′,3,3′,4,5′,6-HeptaCB	40186-70-7	4CL, 2M	7.17	
176	2,2′,3,3′,4,6,6′-HeptaCB	52663-65-7	4CL, 2M	6.76	
177	2,2′,3,3′,4,5′,6′-HeptaCB	52663-70-4	4CL, 2M	7.08	
178	2,2′,3,3′,5,5′,6-HeptaCB	52663-67-9	4CL, 2M	7.14	
179	2,2′,3,3′,5,6,6′-HeptaCB	52663-64-6	4CL, 2M	6.73	

Table 1.3 (continued)

BZ No.	IUPAC name	CAS No.	Descriptor[b]	Log K_{ow}	Vapour pressure (atm at 25 °C)[c]
180	2,2′,3,4,4′,5,5′-HeptaCB	35065-29-3	4CL, PP, 2M	7.36	1.3×10^{-9}
181	2,2′,3,4,4′,5,6-HeptaCB	74472-47-2	4CL, PP, 2M	7.11	
182	2,2′,3,4,4′,5,6′-HeptaCB	60145-23-5	4CL, PP, 2M	7.20	
183	2,2′,3,4,4′,5′,6-HeptaCB	52663-69-1	4CL, PP, 2M	7.20	
184	2,2′,3,4,4′,6,6′-HeptaCB	74472-48-3	4CL, PP	6.85	
185	2,2′,3,4,5,5′,6-HeptaCB	52712-05-7	4CL, 2M	7.11	
186	2,2′,3,4,5,6,6′-HeptaCB	74472-49-4	4CL, 2M	6.69	
187	2,2′,3,4′,5,5′,6-HeptaCB	52663-68-0	4CL, 2M	7.17	
188	2,2′,3,4′,5,6,6′-HeptaCB	74487-85-7	4CL, 2M	6.82	
189	2,3,3′,4,4′,5,5′-HeptaCB	39635-31-9	**CP1, 4CL, PP, 2M**	7.71	
190	2,3,3′,4,4′,5,6-HeptaCB	41411-64-7	4CL, PP, 2M	7.46	
191	2,3,3′,4,4′,5′,6-HeptaCB	74472-50-7	4CL, PP, 2M	7.55	
192	2,3,3′,4,5,5′,6-HeptaCB	74472-51-8	4CL, 2M	7.52	
193	2,3,3′,4′,5,5′,6-HeptaCB	69782-91-8	4CL, 2M	7.52	
194	2,2′,3,3′,4,4′,5,5′-OctaCB	35694-08-7	4CL, PP, 2M	7.80	
195	2,2′,3,3′,4,4′,5,6-OctaCB	52663-78-2	4CL, PP, 2M	7.56	
196	2,2′,3,3′,4,4′,5,6′-OctaCB	42740-50-1	4CL, PP, 2M	7.65	
197	2,2′,3,3′,4,4′,6,6′-OctaCB	33091-17-7	4CL, PP, 2M	7.30	
198	2,2′,3,3′,4,5,5′,6-OctaCB	68194-17-2	4CL, 2M	7.62	
199	2,2′,3,3′,4,5,5′,6′-OctaCB	52663-75-9	4CL, 2M	7.62	
200	2,2′,3,3′,4,5,6,6′-OctaCB	52663-73-7	4CL, 2M	7.20	
201	2,2′,3,3′,4,5′,6,6′-OctaCB	40186-71-8	4CL, 2M	7.27	
202	2,2′,3,3′,5,5′,6,6′-OctaCB	2136-99-4	4CL, 2M	7.24	
203	2,2′,3,4,4′,5,5′,6-OctaCB	52663-76-0	4CL, PP, 2M	7.65	
204	2,2′,3,4,4′,5,6,6′-OctaCB	74472-52-9	4CL, PP, 2M	7.30	
205	2,3,3′,4,4′,5,5′,6-OctaCB	74472-53-0	4CL, PP, 2M	8.00	
206	2,2′,3,3′,4,4′,5,5′,6-NonaCB	40186-72-9	4CL, PP, 2M	8.09	
207	2,2′,3,3′,4,4′,5,6,6′-NonaCB	52663-79-3	4CL, PP, 2M	7.74	
208	2,2′,3,3′,4,5,5′,6,6′-NonaCB	52663-77-1	4CL, 2M	7.71	
209	2,2′,3,3′,4,4′,5,5′,6,6′-DecaCB	2051-24-3	4CL, PP, 2M	8.18	

[a] The nomenclature in this table adheres to the IUPAC rules and thus primed and unprimed numbers may be interchanged compared with Table 1.1. Please see text for more details.

[b] Congener descriptors (CP0, CP1, 4Cl, PP, 2M) have been given where relevant; they give rapid access to geometry and substituent positions. 68 coplanar congeners fall into one of two groups CP0 or CP1.

The first group of 20 congeners consists of those without chlorine substitution at any of the "*ortho*" positions on the biphenyl backbone and are referred to as CP0 or non-"*ortho*" congeners. The second group of 48 congeners includes those with chlorine substitution at only one of the "*ortho*" positions and are referred to as CP1 or mono-"*ortho*" congeners. 175 congeners have a total of four or more chlorine substituents, regardless of position (4Cl). 54 congeners have both "*para*" positions chlorinated (PP). 146 congeners have two or more of the "*meta*" positions chlorinated (2M). The twelve congeners that have all four of the congener descriptors are referred to as being "dioxin-like," and are indicated in bold type.

In ATSDR (2000), PCB-63 was mistakenly attributed the CAS number of a pentachlorobiphenyl; for Henry's law constants, vapour pressure and solubility of most individual congeners, the reader is referred to Dunnivant & Elzerman (1988) and references within.

[c] Vapour pressures have been indicated for a selection of individual congeners.

BZ, Ballschmiter and Zell; CAS, Chemical Abstracts Service; CB, chlorinated biphenyl; IUPAC, International Union of Pure and Applied Chemistry

From Dunnivant & Elzerman (1988), ATSDR (2000), Mills *et al.* (2007), and Lindell (2012)

Table 1.4 The 12 dioxin-like PCBs, with corresponding CAS number, IUPAC name, and individual WHO_{1998}-TEF and WHO_{2005}-TEF values

PCB	IUPAC name	CAS No.	WHO_{1998}-TEF	WHO_{2005}-TEF
PCB-77	3,3′,4,4′-TetraCB	32598-13-3	0.0001	0.0001
PCB-81	3,4,4′,5-TetraCB	70362-50-4	0.0001	0.0003
PCB-105	2,3,3′,4,4′-PentaCB	32598-14-4	0.0001	0.00003
PCB-114	2,3,4,4′,5-PentaCB	74472-37-0	0.0005	0.00003
PCB-118	2,3′,4,4′,5-PentaCB	31508-00-6	0.0001	0.00003
PCB-123	2,3′,4,4′,5-PentaCB	65510-44-3	0.0001	0.00003
PCB-126	3,3′,4,4′,5-PentaCB	57465-28-8	0.1	0.1
PCB-156	2,3,3′,4,4′,5-HexaCB	38380-08-4	0.0005	0.00003
PCB-157	2,3,3′,4,4′,5′-HexaCB	68782-90-7	0.0005	0.00003
PCB-167	2,3′,4,4′,5,5′-HexaCB	52663-72-6	0.00001	0.00003
PCB-169	3,3′,4,4′,5,5′-HexaCB	32774-16-6	0.01	0.03
PCB-189	2,3,3′,4,4′,5,5′-HeptaCB	39635-31-9	0.0001	0.00003

CAS, Chemical Abstracts Service; CB, chlorinated biphenyl; IUPAC, International Union of Pure and Applied Chemistry; PCB, polychlorinated biphenyl; TEF, toxicity equivalency factor
From Van den Berg *et al.* (1998, 2006)

2001; Kania-Korwel & Lehmler, 2013). The IUPAC nomenclature and BZ number for the 19 atropisomeric PCBs are listed in Table 1.5. They are stereoisomers resulting from hindered rotation around single bonds where the steric-strain barrier to rotation is high enough to allow for the isolation of the enantiomers (Haglund & Wiberg, 1996; Harju & Haglund, 1999). Both atropisomers have the same chemical and physical behaviour, except for optical rotation (Lehmler *et al.*, 2010). They are stable at 25 °C, but at elevated temperatures it is necessary to separate the enantiomers via high-resolution chiral gas chromatography (GC) (Schurig & Reich, 1998; Harju & Haglund, 1999).

1.1.2 Chemical and physical properties of PCBs

Pure single PCB congeners are mostly colourless or slightly yellowish, often odourless, crystalline compounds. Commercial products, however, are viscous liquid mixtures of these compounds, with viscosity increasing with degree of chlorination, and colour ranging from light yellow to a dark colour. For example, Aroclor 1242 is a "mobile liquid" and Aroclor 1260 is a "sticky resin" (Erickson, 2001). These products do not crystallize at low temperatures, but turn into solid resins. An important property of PCBs is their general inertness; they resist acids, alkalis and oxidants and are fire-resistant because of their high flash-points (IPCS, 2003). However, under certain conditions, they may be destroyed by chemical, thermal and biochemical processes. PCBs show excellent dielectric (insulating) properties. This has made them useful in a wide variety of applications, including as dielectric fluids in transformers and capacitors, heat-transfer fluids, and lubricants.

The physical properties of PCBs are important in understanding their analytical, physiological, and environmental properties. However, the interactions of the various physical properties can be extremely complex (Erickson, 2001). Chemical and physical properties such as solubility, vapour pressure, and Henry's law constant have been reported for individual congeners (Shiu & Mackay, 1986; Murphy *et al.*, 1987; Sabljić & Güsten, 1989; Dunnivant *et al.*, 1992; Falconer & Bidleman, 1994). Data for homologue groups and for a selection of PCBs are presented in Table 1.2,

Table 1.5 PCB congeners that exist as chiral atropisomers

PCB	IUPAC name
PCB-45	2,2′,3,6-TetraCB
PCB-84	2,2′,3,3′,6-PentaCB
PCB-88	2,2′,3,4,6-PentaCB
PCB-91	2,2′,3,4′,6-PentaCB
PCB-95	2,2′,3,5′,6-PentaCB
PCB-131	2,2′,3,3′,4,6-HexaCB
PCB-132	2,2′,3,3′,4,6′-HexaCB
PCB-135	2,2′,3,3′,5,6′-HexaCB
PCB-136	2,2′,3,3′,6,6′-HexaCB
PCB-139	2,2′,3,4,4′,6-HexaCB
PCB-144	2,2′,3,4,5′,6-HexaCB
PCB-149	2,2′,3,4′,5′,6-HexaCB
PCB-171	2,2′,3,3′,4,4′,6-HeptaCB
PCB-174	2,2′,3,3′,4,5,6′-HeptaCB
PCB-175	2,2′,3,3′,4,5′,6-HeptaCB
PCB-176	2,2′,3,3′,4,6,6′-HeptaCB
PCB-183	2,2′,3,4,4′,5′,6-HeptaCB
PCB-196	2,2′,3,3′,4,4′,5,6′-OctaCB
PCB-197	2,2′,3,3′,4,4′,6,6′-OctaCB

CB, chlorinated biphenyl; IUPAC, International Union of Pure and Applied Chemistry; PCB, polychlorinated biphenyl

Table 1.3, and Table 1.6. Melting points range from 25 °C (PCB-2, PCB-7 and PCB-9) to 306 °C (PCB-209). Boiling points increase from low (monochlorobiphenyl, 285 °C) to highly (decachlorobiphenyl, 456 °C) chlorinated congeners (Hutzinger *et al.*, 1974; Shiu & Mackay, 1986).

The solubility of PCBs in water is extremely low, ranging from an average of 0.0012 to 4830 µg/L for the chlorobiphenyl congeners that occur commonly. The high solubility of the *ortho*-chlorinated congeners (4.8 mg/L for PCB-1) may be due to hydrogen bonding associated with the more polar character of these molecules. Solubility decreases rapidly in *ortho*-vacant congeners, especially as the *para* positions are filled, which may result in greater and more uniform perimeter electronegativity and interference with hydrogen bonding. PCBs are freely soluble in non-polar organic solvents, oils and biological lipids, and the shift from water to lipid solubility is linked to the degree of chlorination (Hutzinger *et al.*, 1974; Shiu & Mackay, 1986; ATSDR, 2000; IPCS, 2003).

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system; values of K_{ow} are thus unitless (Table 1.3 and Table 1.6). The reported log K_{ow} values have been reviewed by Shiu & Mackay (1986). Fig. 1.3 shows the remarkable correlation between log K_{ow} (lipophilicity) and number of chlorine atoms (BZ numbers); log K_{ow} values ranged from 4.5 to 8.3. This partitioning plays a key role in environmental fate and transport. PCBs tend to favour the non-polar phase and will partition away from water to most solids, the organic portion being the preferred site (Erickson, 2001).

PCBs are characterized by Henry's law constants [a measure of the equilibrium distribution coefficient between air and water] that tend to decrease with a higher degree of chlorination. Less chlorinated PCB congeners have a considerably higher vapour pressure (1–2 Pa at 25 °C for monochlorobiphenyls) than the more highly chlorinated congeners (1.4×10^{-6} Pa for decachlorobiphenyl) (Shiu & Mackay, 1986). Therefore, the composition in air is dominated by the less chlorinated congeners and atropoisomers.

At high temperatures, PCBs are combustible, and the products of combustion include polychlorinated dibenzofurans (PCDFs) and hydrogen chloride, and polychlorinated dibenzodioxins (PCDDs) (IPCS, 1993; ATSDR, 2000).

Photochemical degradation may be one route for the breakdown of PCBs in the environment: photochemical experiments conducted under simulated natural conditions on several pure chlorobiphenyls and on commercial PCB products have indicated several degradative reactions, such as dechlorination, polymerization and solvolysis.

Table 1.6 Physical and chemical data for a selection of PCB congeners

PCB	No. of chlorine atoms	Melting point (°C)	Boiling point (°C)	Vapour pressure (10^{-6} kPa at 25 °C)	Log K_{ow}	Water solubility (µg/L)
PCB-1[a]	1	34	274	184	4.5	4830 (25 °C)
PCB-105	5	–	–	0.87	7.0	3.4 (25 °C)
PCB-118	5	–	–	1.20	7.1	13.4 (20 °C)
PCB-138	6	78.5–80	400[b]	0.53	6.5–7.4[b]	15.9[b]
PCB-153	6	103–104	–	0.05	6.7	0.9 (25 °C)
PCB-156	6	–	–	0.21	7.6	5.3 (20 °C)
PCB-163	6	–	–	0.08	7.2	1.2 (25 °C)
PCB-169	6	201–202	–	0.05	7.4	0.04–12.3[b]
PCB-180	7	109–110	240–280 (at 2.66 kPa)	0.13	6.7–7.2[b]	0.2 (25 °C)
PCB-183	7	83	–	–	8.3	4.9 (20 °C)

[a] Included based on its significantly different solubility and vapour pressure
[b] Calculated
K_{ow}, octanol/water partition coefficient; PCB, polychlorinated biphenyl
From Lindell (2012)

1.1.3 *Trade names and composition of commercial products*

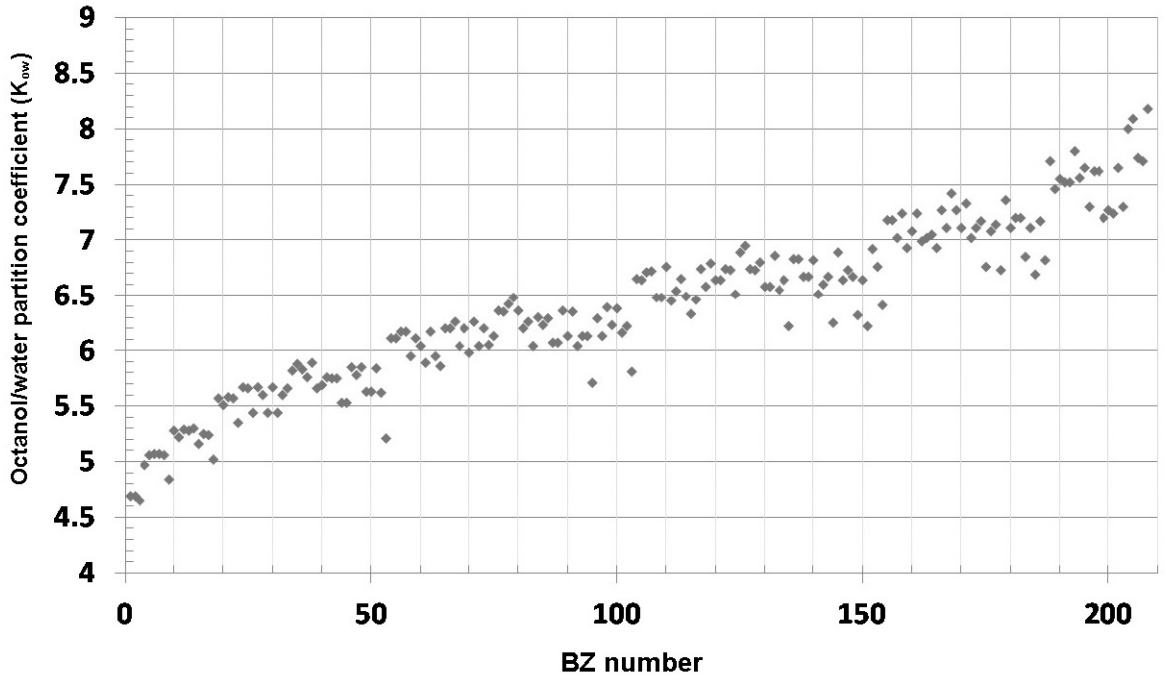
PCBs have never been used as single compounds, but rather as complex mixtures. The commercial products were manufactured to yield a certain degree of chlorination to fulfil technical requirements, generally between 21% and 68% chlorine.

Trade names for commercial products are given in Table 1.7. The most well known are Aroclor, Clophen, Phenochlor, Kanechlor, Pyralene, Fenclor, and Delor. The Aroclors, which were manufactured in the USA, are identified by a four-digit numbering code in which the first two digits indicate the type of mixture and the last two digits indicate the approximate chlorine content by percentage weight. Thus Aroclor 1242 is a chlorinated biphenyl mixture with an average chlorine content of 42%. The exception to this code is Aroclor 1016, which has an average chlorine content of 41% (Hutzinger *et al.*, 1974). Similarly, the Kanechlors are identified by a three-digit value indicating the average chlorine content (300 for 30%). Other products of similar chlorination content have been produced by different companies in Europe, Japan, and China.

Table 1.8 indicates equivalencies between main commercial formulations of PCBs. [The Working Group noted that these should be considered as approximate.] Since different production yield slight differences in the congener mixture, mixtures with comparable chlorine content but from different manufacturers (e.g. Aroclor 1260 and Clophen A60) show varying compositions, although with strong similarities (Johnson *et al.*, 2000).

The homologue composition of the commercial PCB products varies greatly according to chlorination degree achieved (Table 1.9). For example, Aroclor 1242 is a mixture of mono- to heptachlorobiphenyls, while Aroclor 1260 contains penta- to octachlorinated homologues. The concentrations of single congeners within each homologue group also differ between different products and batches (Fig. 1.4). About 130 of the 209 congeners have been identified in commercial formulations at concentrations above 0.05%. Generally, commercial PCB products consist of about 100–140 PCB congeners, with mono- and non-*ortho* substituted PCBs as minor or trace constituents (Frame *et al.*, 1996a, b; Johnson *et al.*, 2000).

Fig. 1.3 Octanol/water partition coefficient (K_{ow}) of PCB congeners according to the degree of chlorination (BZ number)



BZ, Ballschmiter and Zell; PCB, polychlorinated biphenyl
Compiled by the Working Group

An archetypal distribution of PCB congeners was detected in Aroclor 1254, lot 124–191 (corresponding to the historical G4 production process), while lot 6024 showed a profile characteristic of the A4 production process used between 1974 and 1976 (Kodavanti *et al.*, 2001). Indeed, Aroclor 1254 was produced by two different chlorination procedures (two-step versus single-step chlorination) (Frame *et al.*, 1996a, b). The differences in composition of the two lots are given in Table 1.10. Although Aroclor 1254 A4 probably represented less than 1% of the total production of Aroclor 1254, this PCB product was extensively used by standard suppliers and thus by researchers (Frame, 1999).

Chiral PCB congeners are important constituents of both technical and environmental mixtures of PCBs. For example, the total concentration of chiral PCB congeners in the commercial mixtures Aroclor 1242 and Aroclor 1260 is 6% and 30% by weight, respectively (Kania-Korwel *et al.*, 2007). Chiral enantiomers may have different biological and toxicological properties (Püttmann *et al.*, 1989; Rodman *et al.*, 1991). There is evidence that PCB atropisomers differ in their biological activities (Kania-Korwel *et al.*, 2006, 2008). They have been found in non-racemic proportions in many species (Lehmler *et al.*, 2010; Wong & Warner, 2009). While physical and chemical processes in the environment generally affect the two enantiomers of a known compound at the same rate, biological processes may result in the enrichment of one of the enantiomers, because of enantio-selective interactions with biological macromolecules (Buser & Mueller, 1993).

Table 1.7 Trade names for commercial PCB products[a, b]

Asbestol (trans, cap)	Hydol (trans, cap)
Askarel	Montar
Bakola 131 (trans, cap)	Nepolin
Biclor (cap)	No-Flamol (trans, cap)
Chlorextol (trans)	Phenoclor (trans, cap)
Chlorinol	Pydraul
Clophen (trans, cap)	Pyralene (trans, cap)
Clorphen (trans)	Pyranol (trans, cap)
Delor	Pyroclor (trans)
Duconol (cap)	Saf-T-Kuhl (trans, cap)
Dykanol (trans, cap)	Santotherm FR
EEC-18	Santovac 1 and 2
Elemex (trans, cap)	Siclonyl (cap)
Eucarel	Solvol (trans, cap)
Fenchlor (trans, cap)	Sovol
Elemex (trans, cap)	Therminol FR
Hivar (cap)	

[a] Each trade name may correspond to one or several products with varying chlorine content (see Table 1.8).
[b] Products may be used in transformers (trans) or capacitors (cap).
PCB, polychlorinated biphenyl
From IPCS (1993)

1.1.4 *Contaminants and impurities of commercial products*

Commercial PCB products have been reported to be contaminated with other chlorinated aromatic compounds, such as polychlorinated naphthalenes and PCDFs (IARC, 1978). Vos & Koeman (1970) were able to identify tetrachlorodibenzofurans, pentachlorodibenzofurans, and chlorinated naphthalenes in samples of Phenoclor DP-6 and Clophen A60. Bowes *et al.* (1975) examined samples of Aroclor 1248, 1254 and 1260 produced in 1969, samples of Aroclor 1254 from 1970 and Aroclor 1016 from 1972, and samples of Aroclor 1260, Phenoclor DP-6 and Clophen A60. They found PCDFs in all Aroclor preparations except Aroclor 1016, and in Clophen A60 and Phenoclor DP-6 (Table 1.11). The levels of PCDFs were in the low microgram per gram range (Erickson, 2001), but additional PCDFs may be formed from PCBs on heating. Impurities such as 2,3,7,8-tetrachlorodibenzofuran and 2,3,4,7,8-pentachlorodibenzofuran have been reported in different amounts under various manufacturing conditions in Aroclor 1248, Aroclor 1254, Clophen A-60, Phenoclor DP-6, and Kanechlor 400 (de Voogt & Brinkman, 1989). Rappe & Gara (1977) confirmed by capillary gas chromatography–mass spectrometry (GC–MS) that 2,3,7,8-tetrachlorodibenzofuran was one of the main PCDFs in "Yusho oil," as reported by Nagayama *et al.* (1976).

The proportion of impurities may vary between batches. For example, Aroclor 1254 with lot numbers 6024 and 124–191, which were produced by the same company by two different production processes, showed a 3.4-fold difference in the total concentration of PCDFs (Table 1.10).

It is important to note that PCDDs are not found in commercial PCB preparations (Erickson, 2001).

Overall, differences in composition as well as the presence of toxicologically relevant impurities may have had a significant impact on the results of toxicological studies with commercial

Table 1.8 Comparison of commercial PCB products based on percentage chlorination

Average number of chlorine atoms/ molecule	Range of chlorination (%)	Aroclor (USA)	Clophen (Germany)	Phenoclor (France)	Pyralene (France)	Kanechlor (Japan)	Fenoclor (Italy)	Delor (former Czechoslovakia)	PCB (China)
1.15	21	1221							
2	32–33	1232			2000	200			
2.5	38				1500				
3	40–42	1242, 1016	A30	CP3	3000	300	42	2; 103	PCB_3
4	48	1248	A40	DP4		400		3; 104	
5	52–54	1254	A50	DP5		500	54	4 and 5; 105	PCB_5
6–6.8	60–62	1260, 1262	A60	DP6		600	64	106	
8.7	68	1268					70		
10	71	1270					DK		

PCB, polychlorinated biphenyl
Adapted from de Voogt & Brinkman (1989), Erickson (1997), and Johnson *et al.* (2000)

Table 1.9 Homologue composition and physical properties of selected commercial PCB products

	Aroclor							Kanechlor		
	1221	**1232**	**1016**	**1242**	**1248**	**1254**	**1260**	**300**	**400**	**500**
Composition (%)										
Biphenyl	11	6	< 0.01	-	-	-	-	-	-	-
Monochlorobiphenyl	51	26	1	1	-	-	-	-	-	-
Dichlorobiphenyl	32	29	20	17	1	-	-	17	3	-
Trichlorobiphenyl	4	24	57	40	23	-	-	60	33	5
Tetrachlorobiphenyl	2	15	21	32	50	16	-	23	44	27
Pentachlorobiphenyl	0.5	0.5	1	10	20	60	12	0.6	16	55
Hexachlorobiphenyl	-	-	< 0.01	0.5	1	23	46	-	-	13
Heptachlorobiphenyl	-	-	-	-	-	1	36	-	-	-
Octachlorobiphenyl	-	-	-	-	-	-	6	-	-	-
Nonachlorobiphenyl	-	-	-	-	-	-	-	-	-	-
Properties										
Relative molecular mass	200.7	232.2	257.9	266.5		328.0	357.7			
Colour	Clear	Clear	Clear	Clear		Light yellow	Light yellow			
Density (g/cm^3 at 25 °C)	1.18	1.26 1.27	1.37	1.38	1.41 1.44	1.50 1.54	1.56 1.62			
Viscosity (cP at 38 °C)	5	8	20	24	70	700	Resin			
Physical state	Oil	Oil	Oil	Oil		Viscous liquid	Viscous liquid			
Boiling point (°C)	275–320	290–325	325–356	325–366		365–390	385–420			
Water solubility (µg/L at 25 °C)	200 15 000[a]	1450[a]	240 420	240	52 54	12	3			
Vapour pressure (10^{-6} kPa at 25 °C)	893	613	53	53	53	11	5.3			
Henry's law K (atm.m^3/mol, 25 °C)	3.5×10^{-3}		2.9×10^{-4}	5.2×10^{-4}		2.0×10^{-3}	4.6×10^{-3}			
Log K_{ow}[b]	2.8	3.2	4.4	4.1	6.1	6.5	6.9			
Flashpoint (°C)	141–150	152–154	170	176–180	193–196	None to boiling	None to boiling			

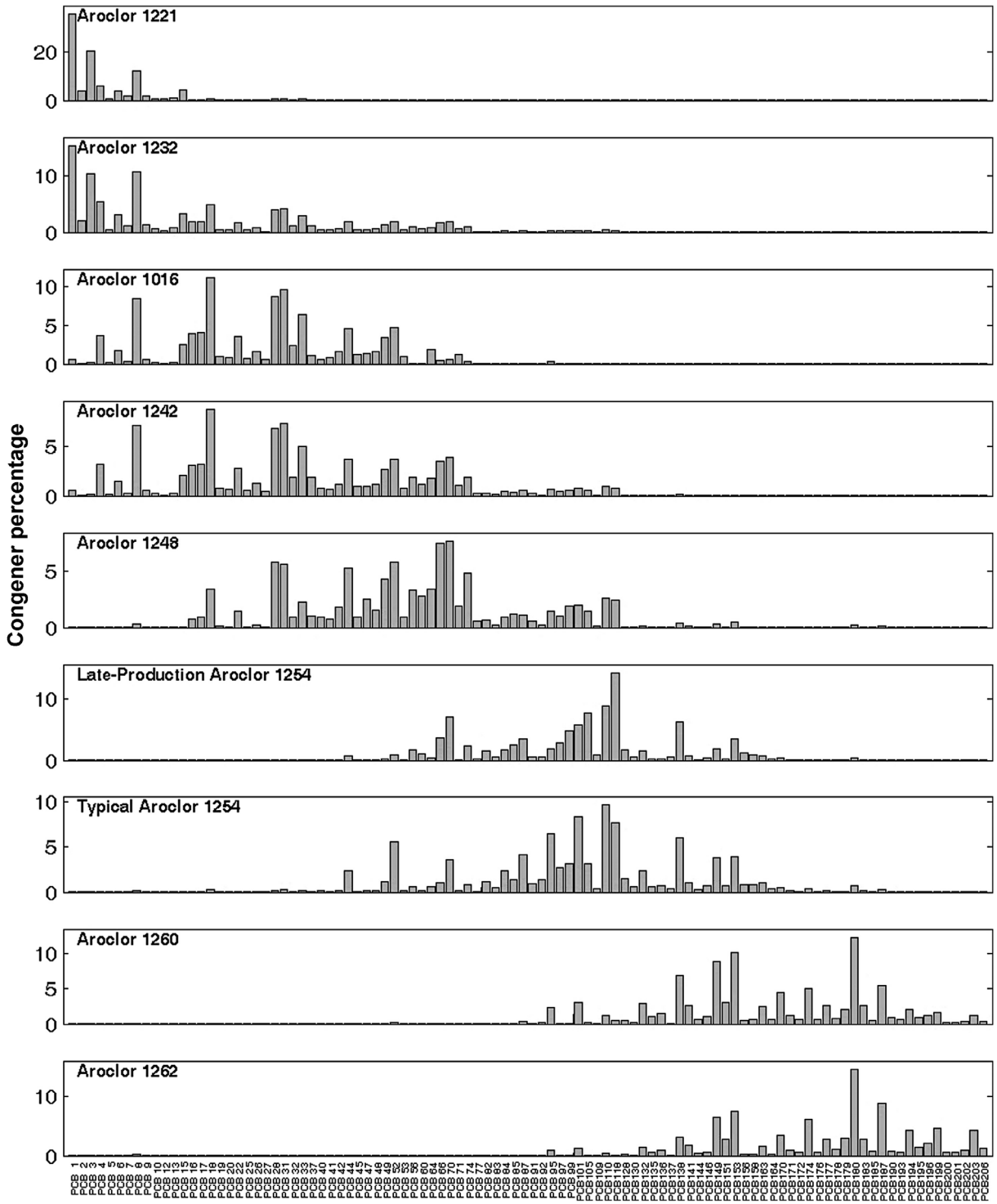
[a] Estimated value

[b] Log K_{ow} represents an average value for the major components of the Arochlor mixture. The Henry's law constants were estimated by dividing the vapour pressure by the water solubility (Cohen & Mercer, 1993; Erickson, 1997).

PCB, polychlorinated biphenyl

From Hutzinger *et al.* (1974), Pellet *et al.* (1993), and Lindell (2012).

Fig. 1.4 Congener-specific composition of Aroclor formulations



Only the 100 most abundant congeners are shown in this figure.
Reprinted from Johnson *et al.* (2000). Copyright (2000), with permission from Elsevier

Table 1.10 Chemical profile and impurities (polychlorodibenzodioxins, polychlorodibenzofurans and polychlorinated naphthalenes) in lots 124–191 and 6024 of Aroclor 1254

PCBs and impurities	Aroclor 1254	
	Lots 124–191 (G4 process)	Lot 6024 (A4 process)
Non-ortho *congeners*		
PCB-77	0.01 mg/g	27.2 mg/g
PCB-81	0.01 mg/g	0.28 mg/g
PCB-126	0.17 mg/g	3.24 mg/g
PCB-169	0.01 mg/g	0.02 mg/g
Mono-ortho *congeners*		
PCB-105	51.00 mg/g	130.00 mg/g
PCB-114	0.05 mg/g	0.78 mg/g
PCB-118	127.00 mg/g	124.00 mg/g
PCB-123	0.57 mg/g	2.14 mg/g
PCB-156	4.80 mg/g	51.00 mg/g
PCB-157	0.36 mg/g	26.30 mg/g
PCB-167	ND	ND
PCB-189	ND	ND
PCDFs		
2,3,7,8-TetraCDF	129.9 ng/g	350.1 ng/g
1,2,3,7,8-PentaCDF	295 ng/g	1920.2 ng/g
2,3,4,7,8-PentaCDF	821 ng/g	4049.2 ng/g
1,2,3,4,7,8-HexaCDF	1638.1 ng/g	4571.4 ng/g
1,2,3,6,7,8-HexaCDF	733.7 ng/g	3190.5 ng/g
1,2,3,7,8,9-HexaCDF	ND	ND
2,3,4,6,7,8-HexaCDF	213.3 ng/g	1333.3 ng/g
1,2,3,4,6,7,8-HeptaCDF	581.8 ng/g	1506.5 ng/g
1,2,3,4,7,8,9-HeptaCDF	533.3 ng/g	1459.4 ng/g
1,2,3,4,6,7,8,9-OctaCDF	356 ng/g	945.6 ng/g
Σ polychlorinated dibenzofurans (PCDF)	11.3 µg/g	38.7 µg/g
Σ polychlorinated dibenzo-p-dioxins (PCDD)	< 2 ng/g	< 2 ng/g
Σ polychlorinated naphtalenes	155 µg/g	171 µg/g
Σ non-*ortho* congeners-TEQ	17.3 µg WHO-TEQ/g	353 µg WHO-TEQ/g
Σ mono-*ortho* congeners-TEQ	5.51 µg WHO-TEQ/g	10 µg WHO-TEQ/g
Σ PCDF-TEQ	0.54 µg WHO-TEQ/g	2.25 µg WHO-TEQ/g
Total PCDD+PCDF+PCB-TEQ	23.4 µg WHO-TEQ/g	365.3 µg WHO-TEQ/g

CDF, chlorodibenzofuran; ND, not detected; PCB, polychlorinated biphenyl; PCDFs, polychlorodibenzofurans; TEQ, toxic equivalent
Adapted from Kodavanti *et al.* (2001) and EFSA (2005)

Table 1.11 Concentrations of chlorodibenzofurans in Aroclor, Clophen, and Phenoclor

Commercial PCB mixture (date of production)	Polychlorodibenzofurans (concentrations in mg/g)			
	Tetra-CDF	Penta-CDF	Hexa-CDF	Total
Aroclor 1248 (1969)	0.5	1.2	0.3	2.0
Aroclor 1254 (1969)	0.1	0.2	1.4	1.7
Aroclor 1254 (1970)	0.2	0.4	0.9	1.5
Aroclor 1260 (1969)	0.1	0.4	0.5	1.0
Aroclor 1260 (lot AK3)	0.2	0.3	0.3	0.8
Aroclor 1016 (1972)	< 0.001	< 0.001	< 0.001	-
Clophen A60	1.4	5.0	2.2	8.6
Phenoclor DP6	0.7	10.0	2.9	13.6

CDF, chlorodibenzofuran
Adapted from Bowes *et al.* (1975)

PCB products and mixtures (EFSA, 2005). Consistent interpretation of the results of such studies, especially differentiation of the effects caused by respective PCBs, may only be achieved if the congener composition of these mixtures is known. The determination of the content in specific congeners was not feasible in most cases due to the lower sensitivity of analytical techniques available in the past.

1.2 Analysis

1.2.1 General considerations

Past and current methods for the chemical analysis of PCBs have been reviewed recently (Le Bizec *et al.*, 2015). Since the 1960s, PCBs have been determined using GC techniques with electron capture detection (ECD), initially using packed columns. Today the separation has been improved by the use of capillary columns and the selectivity by the use of MS detectors. Increase in sensitivity, expressed as decreasing detection limits, has been achieved as analytical techniques have improved.

Originally, PCB concentrations were determined on the basis of commercial products, e.g. various Aroclor products with different chlorination levels. Later, PCB concentrations were determined based on homologue groups, while today congener-specific analysis is a common practice. These methodological changes, including differences in the basis of quantification, are an obstacle when comparing older with more recent studies.

Even when comparing studies from the same period, it can be difficult to compare PCB concentrations reported by different laboratories, if information on data quality is not available and if the results for different numbers of congeners are summarized. Often "total" PCB concentrations are reported, summing up all the congeners included in the laboratory's method and assumed to approach the true total PCB concentration. Operational sum parameters have been defined to harmonize congener lists and improve comparability, for example, the six indicator PCB congeners (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, and PCB-180), expressed as PCB_6. The six congeners were not selected from a toxicological point of view, but were considered as indicators for the different PCB patterns in various sample types and are most suitable for evaluating non-dioxin-like PCBs (NDL-PCBs) (EFSA, 2005). This parameter is used, for example, in the European food and feed regulation (EC, 2011a).

Some agencies, such as the International Council for the Exploration of the Sea (ICES), recommend reporting PCB_7, which includes the

mono-*ortho* congener PCB-118 in addition to the PCB_6 (ICES, 2012; Webster *et al.*, 2013). In the Arctic Monitoring and Assessment Programme (AMAP), the sum of 10 PCB congeners is often reported (PCB-28, PCB-31, PCB-52, PCB-101, PCB-105, PCB-118, PCB-138, PCB-153, PCB-156, PCB-180), which includes the six indicator PCBs. However, reports of individual concentrations in scientific studies have the advantage of allowing sum calculations as required. In food analyses, PCB concentrations are preferred to compliance/non-compliance reports (EFSA, 2005).

Depending on the sample type and the purpose of the study, PCB concentrations may be reported in different units. Concentrations in solid samples are generally reported in mass per mass. Normalizations to dry weight or lipid weight are common for abiotic matrices (e.g. soil and sediment) and those with a high lipid content (e.g. fatty food products), respectively. For liquid and air samples, the concentrations are often given in mass per volume. However, as liquid volumes are susceptible to small changes during sample storage and cannot be determined as precisely as masses, concentrations in small liquid volume samples (e.g. blood) are increasingly related to mass instead of volume.

Apart from the adjustment of mass for fresh weight (also referred to as raw weight, wet weight), lipid normalization of PCB concentrations in blood samples is also common. (Schisterman *et al.*, 2005; Phillips *et al.*, 1989; Grimvall *et al.*, 1997). [The Working Group has acknowledged that a variety of lipid determination methods for blood are used and that there is no consensus on how to determine lipid concentrations.]

Given the low concentrations of PCBs in some matrices, reliable quality assurance and quality control are particularly important, including for example monitoring of recovery rates and procedural blanks, duplicate analyses, analyses of in-house reference material and external quality control in proficiency testing schemes.

The transport and storage of samples can be a source of error through PCB loss or contamination. Studying the effects of storage conditions on PCBs in biological material, De Boer & Smedes (1997) generally did not find temperature effects as long as the temperature was < 5 °C, or downward trends in PCB contents. Practical guidance on the storage and transport of marine samples intended for PCB analysis is given by OSPAR (1999, 2002) and Webster *et al.* (2013).

[The Working Group stressed the importance of how the "non-detects" were reported and treated in the data analysis. There are a variety of methods used and there is currently no global consensus.]

1.2.2 Analytical tools

Instrumental analysis is essentially identical for all matrices. Dioxin-like PCBs (DL-PCBs) are often analysed together with dioxins and furans by gas chromatography-high resolution mass spectrometry (GC-HRMS). For this purpose, DL-PCBs are separated from other PCB congeners as part of the clean-up and fractionation process, for example using activated carbon, porous graphite columns, or 2-(1-pyrenyl) ethyldimethylsilyated (PYE) silica (Hess *et al.*, 1995).

Gas chromatography-electron capture detection (GC-ECD) provides low detection limits and high precision, but is less specific than MS, as it separates PCB congeners only by retention time. MS adds a second dimension in terms of different mass spectra. Therefore, ^{13}C-labelled PCB congeners can be separated from the native molecule on a mass basis. In contrast, as retention times are identical to the native analogues, ^{13}C-labelled PCB congeners cannot be used in GC-ECD analyses.

Due to lower selectivity and the risk of interference, GC-ECD is often based on two GC capillary columns of different polarity (dual column GC) (Covaci & Schepens, 2001). Webster

et al. (2013) recommend that retention times be checked for shifts between analytical runs, usually with the help of characteristic peaks, for example those added as injection standards. Coelution of PCB-138 and PCB-163 occurs on many common capillary columns.

Among the MS techniques, electron capture negative ionization (ECNI) is very sensitive for detection of penta- to decachlorinated PCBs (Webster *et al.*, 2013). However, electron impact (EI) has better selectivity than ECNI and comparable sensitivity when combined with large-volume injection, which requires rigorous sample clean-up (Covaci *et al.*, 2002a). Suitable target and qualifier ions for PCBs are listed by Webster *et al.* (2013).

Some studies have applied gas chromatography-ion trap mass spectrometry (GC-ITMS), for example for the analysis of PCBs in human milk (Gómara *et al.*, 2011). GC-ITMS with its MS/MS option offers increased selectivity while being less expensive than HRMS (Webster *et al.*, 2013). Triple quadrupole mass spectrometry (LRMS/MS) operated in the selected reaction monitoring mode has also been shown to provide selectivity and sensitivity comparable to that of HRMS in food analyses (Ingelido *et al.*, 2012).

Bioassays are an alternative method of determining PCB concentrations and have been suggested as screening tools for monitoring PCDD/Fs and DL-PCBs in foodstuffs by the European Commission Directive 2002/69 (EC, 2002). The dioxin-responsive chemically activated luciferase (CALUX or lux) assay is mechanism-specific and uses the interaction with the aryl hydrocarbon (Ah) receptor. Differences between results of the bioassay and of the conventional targeted high resolution gas chromatography-high-resolution mass spectrometry (HRGC-HRMS) analysis of PCDD/Fs and DL-PCBs have been shown (van Leeuwen *et al.*, 2007), possibly caused by other compounds capable of interactions with the AhR (Vorkamp *et al.*, 2012).

Enzyme-linked immunosorbent assays (ELISA) have been successfully applied to PCB analyses in environmental samples, showing reasonable agreement with conventional GC analyses, but with a high dependence on sample pretreatment (Johnson & Van Emon, 1996; Deng *et al.*, 2002). Recent developments include, for example, immunosensors for applications in situ (Lin *et al.*, 2008) and immunoaffinity chromatography for sample purification (Van Emon & Chuang, 2013).

1.2.3 Analysis of environmental samples

Selected methods for analysis of PCBs in environmental matrices are presented in Table 1.12.

Supplementary material on analysis of PCBs in soil and sediment is available online at: http://monographs.iarc.fr/ENG/Monographs/vol107/suppl_S1.pdf.

(a) Air and dust

Both active and passive sampling are used for PCB analysis in air. Passive sampling has been applied to the analysis of outdoor air using semi-permeable membrane devices (Ockenden *et al.*, 2001) and polyurethane foam (Mari *et al.*, 2008). Vegetation is used as a natural passive sampler, for example tree bark integrating atmospheric PCB concentrations over the life time of the tree (Hermanson and Hites, 1990) or pine needles reflecting up to several years of PCB exposure (Kylin *et al.*, 1994).

Polyurethane foam has also been used for indoor air collection (Hazrati & Harrad, 2006), but active sampling is often the preferred method (EPA, 1999; Kohler *et al.*, 2005). To account for concentration differences and the limited air volume in an indoor setting, outdoor air is usually sampled by high-volume sampling, while low-volume sampling is used for indoor air.

Once retained on a solid matrix (filter, sorbent), PCBs are solvent-extracted using the same techniques as commonly applied for soil,

Table 1.12 Selected methods of analysis of PCBs in environmental matrices

Sample matrix	Sample preparation	Assay method	Detection limit[a]	Reference
Air	Collection on sorbent/filter, solvent extraction, evaporation, acid treatment and/or other clean-up (if necessary), separation of dioxin-like and non-dioxin-like PCBs if required.	GC-ECD; GC-HRMS	0.03–10 pg/m^3; 10 pg/m^3	McConnell *et al.* (1998), Mari *et al.* (2008)
Dust	Sieving of samples (during sampling or afterwards), solvent extraction, evaporation, acid treatment, back extraction, clean-up, evaporation.	GC-MS	NA	Harrad *et al.* (2009)
Water	Liquid-liquid extraction or SPE of unfiltered or filtered water, evaporation, clean-up if necessary. Alternative technique: Passive sampling	GC-ECD; GC-HRMS	0.22–3 ng/L; 0.004–0.5 ng/L	Hope *et al.* (1997), EPA (2008a)
Soil	(Water removal), extraction, evaporation, clean-up, including sulfur removal, separation of dioxin-like and non-dioxin-like PCBs if required.	GC-HRMS	1.5 ng/kg; 0.4–46 ng/kg	Wang *et al.* (2010), EPA (2008a)
Sediment	(Water removal), extraction, possibly in combination with sulfur removal, evaporation, clean-up, including sulfur removal, separation of dioxin-like and non-dioxin-like PCBs if required.	GC-ECD; GC-MS; GC-HRMS	NA; 0.4–46 ng/kg	Webster *et al.* (2013), EPA (2008a)

[a] Detection limits are given for individual PCB congeners

PCB, polychlorinated biphenyl; ECD, electron capture detection; EI, electron impact; GC, gas chromatography; HRMS, high-resolution mass spectrometry; MS, mass spectrometry; NA, not available; SPE, solid-phase extraction

sediment or biota. Before extraction, recovery/internal standards are added, e.g. PCB congeners that are not present in the environment, or ^{13}C-labelled PCB congeners. Extraction is often performed by Soxhlet (EPA, 1999; Menichini *et al.*, 2007). Ultrasonic extraction and pressurized liquid extraction (PLE) have also been described (Aydin *et al.*, 2007; Mari *et al.*, 2008). Barro *et al.* (2005) applied headspace-solid phase micro extraction, which does not involve solvents.

Whether or not clean-up steps are required depends on potential interferences from the matrix (e.g. particles) and co-extracted compounds as well as on expected concentrations. Adsorption chromatography can be applied, for example using alumina (Zhang *et al.*, 2011a) or silica. As all PCB congeners are acid stable, acid treatment is possible.

Dust for PCB analysis has been collected in several ways, for example from the residents' vacuum cleaner bags (Franzblau *et al.*, 2009; Knobeloch *et al.*, 2012), by vacuuming (Wilson *et al.*, 2001; Harrad *et al.*, 2009) and from air conditioning units (Tan *et al.*, 2007). Dust samples originating from vacuum bags might be sieved, but cut-off sizes differ, e.g. 150 µm (Wilson *et al.*, 2001) and 1 mm (Knobeloch *et al.*, 2012) have been described.

Extraction techniques are basically the same as described for sorbents, including Soxhlet extraction (Dirtu & Covaci, 2010), PLE (Harrad *et al.*, 2009) and ultrasonic extraction (Wilson *et al.*, 2001). Before extraction, internal/recovery standards should be added, as described for air samples. Due to interferences from the matrix and co-extraction of other compounds, clean-up of dust samples will be required. PLE can be combined with simultaneous clean-up by adding adsorption materials to the cells; however, additional clean-up steps may be necessary (Harrad *et al.*, 2009). Various sorbents have been used for clean-up of dust samples, including Florisil (Wilson *et al.*, 2001; Harrad *et al.*, 2009), silica gel (Dirtu & Covaci, 2010), and combinations of both (Knobeloch *et al.*, 2012). As described for air samples, acid treatment has also been applied (Harrad *et al.*, 2009).

(b) Water

The PCB content in a water sample is strongly influenced by the amount of suspended particulate matter (SPM) that adsorbs PCBs. Depending on the objectives of the analysis, different approaches can be chosen, resulting in different fractions to be analysed:

- Unfiltered water includes dissolved components and those bound to colloids and SPM.
- Filtered water gives PCB concentration on SPM (residue on the filter) and dissolved or bound to colloids (filtrate).
- Passive sampling targets the dissolved fraction.

Passive sampling devices integrate PCB concentrations over time, which reduces temporal variability. Common formats for water sampling include semipermeable membrane devices, low density polyethylene, and silicone rubber (Lohmann *et al.*, 2012). Passive sampling techniques have been applied for analysis of PCBs in river water (Grabic *et al.*, 2010) and seawater (Granmo *et al.*, 2000; Fernandez *et al.*, 2012).

In water bodies with a low SPM content, e.g. seawater, PCB concentrations will likely be low, and large amounts of water will have to be sampled and processed, while avoiding contamination. Guidelines for seawater sampling and the subsequent analysis of organic contaminants have been established by OSPAR (OSPAR, 2013). Studies have shown that the critical part of such analysis occurs outside the laboratory, i.e. during sampling, transport, and storage (Wolska *et al.*, 2005). As described for air and dust, recovery/internal standards should be added before extraction.

PCBs from water samples are typically extracted by either liquid–liquid extraction (LLE), i.e. the direct extraction of PCBs with a non-polar solvent (Hope *et al.*, 1997), or solid-phase extraction (SPE), where PCBs are retained on a solid phase and subsequently eluted with a non-polar solvent (Russo *et al.*, 1999). The United States Environmental Protection Agency (EPA) method 1668B for determination of PCBs in several matrices describes SPE, continuous LLE, and separatory funnel extraction as suitable extraction methods for aqueous samples (EPA, 2008a).

The amount of SPM in the sample is a critical factor, as LLE might be insufficient and SPE cartridges might become blocked by samples with a high SPM content (Erger *et al.*, 2012). Alternatively, SPM might be removed by filtration and analysed separately, for example by Soxhlet or ultrasonic extraction. This could be the method of choice for water samples with a high SPM content, for example wastewater samples or landfall leachate (Zorita & Mathiasson, 2005).

To what extent purification is necessary depends on the nature of the sample, its SPM content, PCB concentration and that of interfering compounds. Although sampling only freely dissolved PCBs, some passive sampling approaches add a clean-up step after extraction, for example using acid silica or aluminium (Grabic *et al.*, 2010). Surface-water samples, however, have often been analysed without clean-up (Hope *et al.*, 1997; Erger *et al.*, 2012), while other studies have included adsorption chromatographic steps (Khim *et al.*, 2001). Gel permeation chromatography (GPC) may be used for water extracts that contain organic compounds of high relative molecular mass (EPA, 2008a).

PCB exposure from snow can be considered insignificant, with the exception of polar regions where snow may be a source of drinking-water. Analytical methods are similar to those for water (Carrera *et al.*, 1998).

1.2.4 Analysis of biological samples

Several matrices have been analysed to determine internal exposure to PCBs, or body burden, including adipose tissue, meconium, placenta, blood, umbilical cord blood, human milk, and hair (Table 1.13).

(a) Tissues (adipose tissue and placenta)

The analytical methods applied to the analysis of PCBs in tissues such as adipose and placenta are similar to those used for environmental samples. The characteristically high lipid content of adipose and other tissues, however, requires rigorous lipid removal before instrumental analysis.

Different ways of sample pretreatment have been applied after or as part of the homogenization procedure, for example sample drying with Na_2SO_4 or hydromatrix (Covaci *et al.*, 2002a; Saito *et al.*, 2004), melting of fat (De Saeger *et al.*, 2005), mixing with base (Kim & Fisher, 2008) and addition of ethanol for protein precipitation (Whitcomb *et al.*, 2005).

Extraction is generally carried out with a non-polar solvent such as toluene or hexane, in some cases in a mixture with acetone, dichloromethane or propanol (Guvenius *et al.*, 2002; Saito *et al.*, 2004; Fernandez *et al.*, 2008). The extraction could often proceed by shaking or rotating, for example in an Ultra Turrex or Vortex (Guvenius *et al.*, 2002). Other extraction techniques are the same as those applied in environmental analyses, including ultrasonic extraction (Suzuki *et al.*, 2005), Soxhlet (Fernandez *et al.*, 2008), PLE (Saito *et al.*, 2004), and MAE (Li *et al.*, 2006). Supercritical fluid extraction with carbon dioxide (sometimes modified with dichloromethane) has also been applied (Stellman *et al.*, 1998). For the extraction of placenta, Gómara *et al.* (2012) additionally described the preparation of a suspension that was liquid–liquid extracted. As for other matrices, recovery/internal standards are generally added before extraction.

Table 1.13 Selected methods for analysis of PCBs in biological matrices

Sample matrix	Sample preparation	Assay method	Detection limit[a]	Reference
Adipose tissue	Pre-treatment (drying and/or protein denaturation), extraction, evaporation, lipid removal, further clean-up, separation of dioxin-like and non-dioxin-like PCBs if required.	GC-ECD; GC-HRMS	0.009–1.1 ng/g lipid; 0.002–0.2 ng/g lipid	Whitcomb *et al.* (2005), Fernandez *et al.* (2008)
Placenta	Pretreatment (drying and/or protein denaturation), extraction, evaporation, lipid removal, further clean-up, separation of dioxin-like and non-dioxin-like PCBs if required.	GC-ECD; GC-MS (ECNI)	NA	Gómara *et al.* (2012), Ma *et al.* (2012)
Blood	Protein denaturation, extraction, evaporation, lipid removal, further clean-up, separation of dioxin-like and non-dioxin-like PCBs if required.	GC-ECD; GC-MS; GC-HRMS	10–100 pg/mL; 2–5 pg/mL	Covaci & Schepens (2001), Lu *et al.* (2012)
Urine (hydroxylated PCBs)	Acidification, extraction, evaporation, derivatization.	GC-MS (EI)	0.02–0.04 ng/mL	Hong *et al.* (2005a, b)
Human milk	Drying or protein denaturation + fat globules dispersion, extraction, evaporation, lipid removal, further clean-up, separation of dioxin-like and non-dioxin-like PCBs if required.	GC-ECD; GC-MS; GC-HRMS	NA; 0.01–0.03 ng/mL; NA	Duarte-Davidson *et al.* (1991), Covaci *et al.* (2001), Fürst (2006)
Hair	Washing, incubation with HCl, extraction, evaporation, lipid removal, further clean-up.	GC-ECD; GC-MS (EI)	0.3–2 ng/g	Covaci *et al.* (2002b)

[a] Detection limits are given for individual PCB congeners

ECD, electron capture detection; ECNI, electron capture negative ionization; EI, electron impact; GC, gas chromatography; HCl, hydrochloric acid; HRMS, high-resolution mass spectrometry; MS, mass spectrometry; NA, not available

A common method for lipid removal is treatment of the sample with acid, usually sulfuric acid (Whitcomb *et al.*, 2005). GPC is another suitable method (Ma *et al.*, 2012), but may not achieve complete removal of lipids. The use of partially deactivated neutral aluminium for lipid removal has also been described (Stellman *et al.*, 1998).

For further clean-up of the extracts, the same techniques are applied as in the environmental analyses, either individually or in combinations. These include silica gel (Suzuki *et al.*, 2005; Fernandez *et al.*, 2008), alumina (Covaci *et al.*, 2002a), Florisil (Whitcomb *et al.*, 2005) and GPC (Saito *et al.*, 2004). Impregnating the silica gel with acid is a common way of combining adsorption chromatography with lipid removal (Covaci *et al.*, 2002a; Fernandez *et al.*, 2008).

Some studies have analysed PCB metabolites in adipose tissue and placenta, e.g. hydroxylated PCBs and methylsulfonyl-PCBs. These methods usually included a fractionation by adsorption chromatography and elution with different solvents (Guvenius *et al.*, 2002; Saito *et al.*, 2004). In the method by Gómara *et al.* (2012), hydroxylated PCBs were separated from the parent compounds during liquid-liquid extraction (LLE). After derivatization, the fraction containing hydroxylated PCBs was cleaned up in the same way as described for the parent compounds.

(b) Blood (including umbilical cord blood)

Numerous studies have analysed PCBs in blood, mostly in serum, but also in plasma (Schettgen *et al.*, 2011). The analytical methods used generally do not differ for serum and plasma. Given the low lipid content of blood, PCB concentrations are generally low and the sample amount available for analysis may be a challenge. Most studies work with volumes of 0.5–2 mL. Methods have recently been developed to extract PCBs from only 50 µL of plasma and from dried blood spots (Lu *et al.*, 2012).

Umbilical cord blood has often been analysed in combination with maternal blood, using the same methods. Given the lower lipid content and usually lower PCB concentrations in cord blood, adjustments of the sample intake might be useful; however, sample availability is usually the limiting factor.

Apart from the addition of internal standards, the first step in PCB analysis of serum, plasma or cord blood is generally the denaturation of protein, e.g. by addition of formic acid (Kang *et al.*, 2008), methanol (Korrick *et al.*, 2000), or acetonitrile (Agudo *et al.*, 2009). Different extraction techniques have been described, among which the simple mixing of the sample with solvent (Apostoli *et al.*, 2005; Schettgen *et al.*, 2011). LLE has also been used (Kawashiro *et al.*, 2008; Bachelet *et al.*, 2011) as well as SPE on C_{18} or hydrophilic–lipophilic balanced reversed phase sorbent (Covaci & Schepens, 2001; Lee *et al.*, 2011). Guvenius *et al.* (2003) used Lipidex 5000, a lipophilic gel, for extraction of PCBs from cord blood.

Since they are present at low concentration, lipids are not always removed from the extract (Lu *et al.*, 2012). Lipids can be removed by direct addition of acid to the extracts (Atuma & Aune, 1999) or by clean-up methods on acidified silica (Covaci & Schepens, 2001). Further clean-up sorbents include Florisil (Whitcomb *et al.*, 2005), alumina (Stellman *et al.*, 1998), neutral silica gel (Atuma & Aune, 1999), or combinations of these (Guvenius *et al.*, 2003; Apostoli *et al.*, 2005).

To account for the low concentrations of PCBs in blood, extracts are often reduced to very small volumes, e.g. 50 µL (Covaci & Schepens, 2001). This is achieved by addition of non-volatile keepers (Covaci & Schepens, 2001), or by evaporation to dryness (Apostoli *et al.*, 2005) and reconstitution in the desired solvent or a solution of syringe standards in this solvent. Evaporation to dryness carries the risk of loss of volatile PCB congeners.

Hydroxylated PCB metabolites have been analysed in blood and umbilical cord blood. Guvenius *et al.* (2003) used the same extraction method as for parent PCBs, but obtained hydroxylated PCBs in an isolated fraction, based on different elution solvents. Park *et al.* (2009) treated the sample with hydrochloric acid and 2-propanol, and extracted hydroxylated PCBs by LLE. Hydroxylated PCBs require derivatization to non-polar molecules before separation by GC (Sandau *et al.*, 2000).

(c) Urine

A few studies have assessed PCB metabolites (hydroxylated PCBs) in urine samples. Hydroxylated PCBs are more polar than their parent compounds and act as weak acids, which has to be taken into account in extraction, clean-up, and separation by GC.

Hong *et al.* (2005a, b) presented two methods for the extraction of hydroxylated PCBs from urine. The first method combined SPE testing of four different phases, with five derivatization methods. Best recoveries and GC separations were found for hydroxylated PCBs extracted on a C_2 phase and derivatized with iodopropane under basic conditions (Hong *et al.*, 2005a). The second method used headspace solid-phase microextraction and on-fibre derivatization, achieved by placing the needle in the headspace of a solution of bis(trimethylsilyl)trifluoroacetamide (BSTFA) (Hong *et al.*, 2005b). The derivatized hydroxylated PCBs were transferred to the GC injector by thermic desorption. Several fibre materials were tested, of which polydimethylsiloxane-divinylbenzene (PDMS-DVB) gave the highest signal in the analysis.

(d) Human milk

Breast milk is the most extensively analysed matrix for the estimation of PCB body burden in humans. The first studies date back to the 1970s (Musial *et al.*, 1974), and programmes for the biomonitoring of human milk have been established in several countries or regions (Wilhelm *et al.*, 2007; Krauthacker *et al.*, 2009; Cerná *et al.*, 2012). Analytical methods are very diverse: the milk samples may be treated as liquid, or the lipid phase may be isolated, or the sample may be freeze-dried and treated as solid.

When the whole milk sample is treated as a liquid, the first steps usually include protein denaturation and dispersion of fat globules by addition of sodium oxalate, or acetic acid and methanol, sometimes in combination with ultrasound treatment (Dmitrovic & Chan, 2002; Fürst, 2006). Before or after this step, internal standards are usually added, and the sample is extracted by LLE (Chovancová *et al.*, 2011), or SPE (Covaci *et al.*, 2001; Dmitrovic & Chan, 2002). Hexane is a commonly used solvent, although a large variety of solvent combinations and solvent sequences have been described in the literature.

In some studies, the lipid phase of the milk sample is separated or extracted and a defined amount of fat used for further analysis (Fürst, 2006; Pérez *et al.*, 2012).

In the third approach, milk samples are freeze-dried and a defined amount is extracted with techniques commonly applied to solid samples, e.g. Soxhlet extraction (Duarte-Davidson *et al.*, 1991) and PLE (She *et al.*, 2007). Matrix solid-phase dispersion has also been described (Gómara *et al.*, 2011). However, freeze-drying always runs the risk of loss of volatile PCBs and cross-contamination.

As described for other human matrices, lipids in the extract are removed before instrumental analysis. Furthermore, the extracts usually contain co-extracted compounds that are likely to interfere with PCBs in the instrumental analysis. The clean-up techniques therefore generally include lipid destruction by acid treatment, either directly in the extract (Duarte-Davidson *et al.*, 1991), or by acidified silica gel (Covaci *et al.*, 2001). Alternatively, GPC has been used, but usually in combination with acid treatment (She *et al.*, 2007). Further clean-up techniques include

adsorption chromatography on neutral or basic silica (She *et al.*, 2007), alumina (Chovancová *et al.*, 2011), and Florisil (Pérez *et al.*, 2012), also in combinations (Fürst, 2006). Ingelido *et al.* (2007) described clean-up by supercritical fluid extraction.

(e) Human hair

With a lipid content of about 2% (Altshul *et al.*, 2004), hair accumulates lipophilic compounds such as PCBs and has the advantage of being sampled non-invasively. However, to what extent hair PCB content reflects internal exposure to PCBs is difficult to determine, even if the hair is washed before analysis to avoid co-extraction of dust particles. Comparisons of serum and hair samples showed weak correlations for most PCB congeners and considerably higher PCB concentrations in hair, also on a lipid-normalized basis (Altshul *et al.*, 2004). Effects of hair colour (natural or dyed) cannot be ruled out (Covaci *et al.*, 2002b).

Sample amounts of less than 1 g are sufficient for detection of PCBs. The hair samples are washed, and cut or pulverized, and then spiked with internal or recovery standards and incubated with hydrochloric acid (Covaci *et al.*, 2002b). Extraction techniques applied in hair analyses include LLE (Covaci *et al.*, 2002b), Soxhlet (Zhang *et al.*, 2007), and ultrasonic extraction (Barbounis *et al.*, 2012). The same methods for lipid removal and extraction clean-up as for other biological matrices have been used, e.g. adsorption chromatography on acidified silica gel, alumina (Covaci *et al.*, 2002b), and Florisil (Zhang *et al.*, 2007). A comparison between three laboratories analysing the same hair sample but using different internal standards, extraction techniques and analytical instruments (GC-ECD, GC-LRMS and GC-HRMS) showed good agreement, with a relative standard deviation of 15% (Gill *et al.*, 2004).

1.2.5 Analysis of food samples

Food items are regularly analysed for PCBs in various national and international food-monitoring programmes (Fromberg *et al.*, 2011; EFSA, 2005), and market-basket or duplicate-diet studies have been performed to identify PCB intake from food (Voorspoels *et al.*, 2008; Fromme *et al.*, 2009).

These studies have often applied methods that are sufficiently versatile to allow analysis of different kinds of food item with varying lipid content and consistency. The first step is often a drying of the food material with sodium sulfate (Voorspoels *et al.*, 2008; Schecter *et al.*, 2010), followed by the addition of recovery or internal standards, and Soxhlet extraction using hexane:acetone (Voorspoels *et al.*, 2008), or toluene (Kiviranta *et al.*, 2004). The clean-up usually includes lipid removal by acid treatment, either as direct addition to the extracts (Fromme *et al.*, 2009), or via acid-impregnated silica gel (Voorspoels *et al.*, 2008). Further clean-up steps can include neutral and basic silica gel (Son *et al.*, 2012), alumina (Kiviranta *et al.*, 2004), and Florisil (Schecter *et al.*, 2010); however, the extent of purification and fractionation is highly dependent on the target analytes.

Food monitoring sometimes focuses on DL-PCBs, which are analysed together with dioxins and furans. These are separated from other PCB congeners by fractionation on a carbon column, which separates the molecules by planarity (Fernandes *et al.*, 2004). Given the low concentrations of DL-PCBs, the fractions are sometimes further purified before instrumental analysis (Fromme *et al.*, 2009).

Some studies have used more specific methods for different food items, for example, protein denaturation and dispersion of fat globules in dairy products, by the addition of sodium oxalate, or potassium oxalate and ethanol (Fromberg *et al.*, 2011; Sirot *et al.*, 2012), followed by LLE. In other studies using cows' milk, the samples

are freeze-dried before extraction (Lake *et al.*, 2013), or the fat is separated using a detergent (Pérez *et al.*, 2012). The clean-up steps may be the same as for other lipid-containing matrices. For the analysis of butter and vegetable oil, Roszko *et al.* (2012) described a dialysis method based on low-density polyethylene semi-permeable membranes, followed by GPC and common column clean-up.

Numerous studies have dealt with analysis of PCBs in fish, as summarized by Domingo & Bocio (2007). Analyses of meat and fish basically follow the same methods (Su *et al.*, 2012). Samples are often dried as the first step, e.g. by freeze-drying (Abalos *et al.*, 2010; Liu *et al.*, 2011) or addition of anhydrous sodium sulfate (de Boer *et al.*, 2010). After addition of internal standards, the samples are extracted on a Soxhlet apparatus (Su *et al.*, 2012), by PLE (Pérez-Fuentetaja *et al.*, 2010), or ultrasonic extraction (Son *et al.*, 2012). The clean-up techniques are the same as described for other food matrices, including acid treatment (Su *et al.*, 2012), acid and neutral silica gel, and alumina (Liu *et al.*, 2011), and Florisil (Villa *et al.*, 2011), sometimes in an automated PowerPrep system (Abalos *et al.*, 2010). A rapid extraction and purification method was presented by Kalachova *et al.* (2011), combining PCB partitioning into ethyl acetate and lipid removal on a silica gel microcolumn.

Eggs are commonly analysed for PCBs, with a focus on the egg yolk (Kiviranta *et al.*, 2004; Voorspoels *et al.*, 2008). While the same methods could be applied as for other food samples, recent publications have only equilibrated the sample with solvents (Fromberg *et al.*, 2011; Rawn *et al.*, 2012). The clean-up steps include lipid removal by direct acid treatment and adsorption chromatography on acid silica and Florisil (Rawn *et al.*, 2012).

Fruit and vegetables are analysed less frequently than lipid-rich food items. In the methods described by Grassi *et al.* (2010) and Sirot *et al.* (2012), freeze-drying, extraction using Soxhlet or PLE, and acid treatment were applied, in a manner very similar to that used for analyses of other food items.

1.3 Production and uses

1.3.1 Production processes

PCBs have commonly been synthesized commercially by catalytic chlorination of biphenyl. The catalysts used include iron, iodine, and chlorides of aluminium, tin, and antimony. The synthesis is performed as a one-step chlorination process, or in two steps with further chlorination of residues from the first step. The crude products are purified by alkali wash to remove hydrogen chloride and ferric chloride, blown with air, and sometimes also by distillation (IARC, 1978). The degree of chlorination is controlled by the time (range, 12–36 hours) in the reactor.

The manufacturing process for Aroclors involved the chlorination of biphenyl with anhydrous chlorine in the presence of a catalyst, such as iron filings or ferric chloride. In 1974–1977, "late production" Aroclor 1254 was made by a two-stage chlorination procedure. In the first stage, biphenyl was chlorinated to 42% chlorine content by weight as for Aroclor 1242. This was then fractionated to give a distillate (Aroclor 1016). The residue (mostly mono-*ortho* tetrachlorobiphenyls and higher homologues) was further chlorinated to 54% chlorine by weight, resulting in a lot (Monsanto lot KI-02–6024) with markedly higher levels of the high non-*ortho* and mono-*ortho* PCB congeners than the Aroclor 1254 lots produced earlier. The differences between the early and late lots of Aroclor 1254 are discussed in more detail above (see Section 1.1.3 and Table 1.10).

1.3.2 Production volumes and trends

Although the commercial production of PCBs began in the 1920s, it was not until after 1945 that production reached substantial volumes. Production peaked in the 1960s and 1970s, and had ceased in most countries by the end of the 1970s or early 1980s.

Estimates of the total cumulative worldwide production of PCBs indicate that 1 to 1.5 million tonnes (or more) of commercial PCB products were manufactured. Production volumes from former Czechoslovakia, France, Germany, Italy, Japan, China, Poland, the Russian Federation and the former Soviet Union, Spain, the United Kingdom, and the USA, as reported by Tatsukawa (1976), de Voogt & Brinkman (1989), Jiang *et al.* (1997), AMAP (2000), Holoubek *et al.* (2001a), and Sułkowski *et al.* (2003), add up to around 1 325 000 tonnes for 1930–1993 (Table 1.14).

In the USA, annual production peaked in 1970 with a total volume of 39 000 tonnes. From 1957 to 1971, 12 different types of Aroclor with chlorine contents ranging from 21% to 68% were produced in the USA by Monsanto Chemicals Co. (see Section 1.1). In addition, Geneva Industries produced a smaller amount of PCBs from 1972 to 1974 (EPA, 2008b).

In China, the production of PCBs began in 1965 and was gradually stopped between 1974 and the 1980s. According to preliminary investigation and analysis, 7000–10 000 tonnes of PCBs were produced in China from 1965 to 1974, with 9000 tonnes as PCB_3 [similar to Aroclor 1242] and 1000 tonnes as PCB_5 [similar to Aroclor 1254] (Xing *et al.*, 2005; NIP China, 2007).

Information from the Democratic People's Republic of Korea (NIP Korea DPR, 2008) indicated that production of PCBs has been ongoing at two sites since the 1960s. The initial production capacity for PCBs was 1200 tonnes per year, with a tendency to increase until the 1980s; however, capacity has decreased since the early 1990s, and the average annual production volume in 2001–2006 was 411.6 tonnes. The total amount produced up to 2006 could be estimated at around 30 000 tonnes. According to this report, the Democratic People's Republic of Korea planned to reconsider its production of PCBs in 2012.

The commercial products were marketed under more than one hundred different trade names, depending on place of manufacture, production process, and chlorine content. Aroclors comprised at least 10 different commercial PCB products, under the names Aroclor 1016, 1221, 1232, 1242, 1248, 1254, 1260, 1262, 1268, and 1270. It should be noted that Aroclor 5460 was not a PCB product, but consisted of polychlorinated terphenyls. Other commercial PCB products include Clophen (four products), Delor (three products), Fenclor (five products), Kanechlor (five products), Phenochlor (four products), Pyralene (three products), Sovol, and Therminol (see Section 1.1.3).

1.3.3 Uses

Due to the physical and chemical properties of PCBs, such as non-flammability, chemical stability, high boiling point, and high dielectric constants, PCBs were widely used in several industrial and commercial open and closed applications (Table 1.15). PCBs have also been used in corresponding military applications, but detailed information on military use is typically very scarce.

As a result of the production process, PCBs were never used as individual congeners, but as technical products composed of multiple congeners. The commercial PCB products were generally used as such, but mixtures with other compounds were also produced to obtain specific properties. For example, the PCB product Sovol may have been mixed with α-nitronaphtalene to increase volatility, and sold as Nitrosovol (UNEP, 1988). Similarly, Galbestos was a mixture of PCBs and asbestos used on galvanized steel and

Table 1.14 Volume and duration of PCB production in countries with known production (by production volume)

Producer	Country	Duration		Volume (tonnes)	Reference
		Start	Stop		
Monsanto	USA	1930	1977	641 246	de Voogt & Brinkman (1989)
Bayer AG	Germany, western	1930	1983	159 062	de Voogt & Brinkman (1989)
Orgsteklo	Russian Federation	1939	1990	141 800	AMAP (2000)
Prodelec	France	1930	1984	134 654	de Voogt & Brinkman (1989)
Monsanto	United Kingdom	1954	1977	66 542	de Voogt & Brinkman (1989)
Kanegafuchi	Japan	1954	1972	56 326	Tatsukawa (1976)
Orgsintez	Russian Federation	1972	1993	32 000	AMAP (2000)
Caffaro	Italy	1958	1983	31 092	de Voogt & Brinkman (1989)
2.8 Vinalon and the Sunchon Vinalon Complex	Democratic Republic of Korea	1960[a]	2012[b]	30 000[c]	NIP Korea DPR (2008)
SA Cros	Spain	1955	1984	29 012	de Voogt & Brinkman (1989)
Chemko	Former Czechoslovakia	1959	1984	21 482	Schlosserová (1994)
Xi'an	China	1965	1980	10 000	Jiang *et al.* (1997), NIP China (2007)
Mitsubishi	Japan	1969	1972	2 461	Tatsukawa (1976)
Electrochemical Co.	Poland	1966	1970	1 000	Sułkowski *et al.* (2003)
Zaklady Azotowe Tarnow-Moscice	Poland	1974	1977	679	Sułkowski *et al.* (2003)
Geneva Industries	USA	1972	1974	454	EPA (2008b)
Total		*1930*	*2012*	*1 355 810*	

[a] During the 1960s
[b] "The Ministry of Chemical Industry will, by 2012, take measures to dismantle the PCBs production process and establish a new process of producing an alternative."
[c] Estimated from Republic of Korea 2008, National Implementation Plan for the Stockholm Convention on Persistent Organic Pollutants.
PCB, polychlorinated biphenyl
Adapted from Breivik *et al.* (2007)

galvanized corrugated sliding panels in various industrial and military applications.

(a) Closed applications

The predominant applications for PCBs were in dielectric fluids in capacitors and transformers. These applications are considered to be closed applications, since PCBs are not expected to leak out of the system. However, transformers had occasionally to be topped up with PCBs so that these systems were not completely closed.

While applications in hydraulic and heat transfer, and cooling systems are also usually considered to be closed applications, there have been reports of accidental leaks from such systems, and thus these applications are often referred to as "normally closed."

During the 1960s, dielectric fluid in capacitors and transformers represented 50–60% of the sales of PCBs in the USA (IARC, 1978). In 1972, Monsanto restricted its sale of PCBs to capacitor and transformer applications (Erickson, 2001); after this date, these applications represented some 99% of the total use of PCBs in the USA (Durfee *et al.*, 1976). In China, PCB_3 [similar to Aroclor 1242] was used primarily in power capacitors applied in electricity production, distribution and transmission, while PCB_5 [similar to Aroclor 1254] was used mainly as a paint additive (see Table 1.8).

Table 1.15 Industrial uses of PCBs

System/category	Aroclor									DecaCB
	1221	1232	1016	1242	1248	1254	1260	1262	1268	
Dielectric fluids										
Capacitors	✓		✓+	✓+		✓				
Transformers			✓	✓		✓+	✓+			
Hydraulic/lubricants/heat-transfer fluids										
Heat transfer				✓	✓	✓				
Hydraulic fluids		✓		✓	✓	✓	✓			
Vacuum pumps					✓	✓	✓			
Gas transmission turbines	✓			✓						
Immersion oil for microscopes							✓			✓
PCBs incorporated into products and materials										
Rubber	✓	✓		✓+	✓	✓			✓	
Synthetic resins					✓	✓	✓	✓	✓	
Carbonless copy paper				✓+						
Pipeline valve grease									✓	
Adhesives	✓	✓		✓+	✓	✓				
Wax extenders				✓+		✓			✓	
Caulk and joint sealants						✓[a]				
Insulation and other building materials						✓			✓	
De-dusting agents						✓	✓			
Inks						✓				
Cutting oils						✓				
Wire and cable coatings						✓	✓			
Die or investment casting										✓
Pesticide extenders						✓				

[a] Also others
✓ Denotes use of given Aroclor in a specific end-use
✓+ Denotes principal use
PCB, polychlorinated biphenyl
Adapted from Johnson *et al.* (2000) and Erickson & Kaley (2011)

As production and use of PCBs became banned, outdated PCB-containing equipment (equipment filled with PCBs as dielectric fluid) was generally removed from use and stored for disposal (Xing *et al.* 2005). In this equipment, about 6000 tonnes of PCBs came from capacitors (NIP China, 2007).

(b) Open applications

PCBs were also used in several open applications as a major constituent of permanent elastic sealants and as flame-retardant coatings (Heinzow *et al.*, 2007).

The use as plasticizer in sealants (caulking material) and flooring material was common in many countries, representing up to 15–20% of the total use of PCBs in Sweden (Jansson *et al.* 1997). The sealants were mainly used in outdoor applications, but indoor use was not uncommon. Use in flooring material was limited to indoor use.

Sealants that were mixed with PCBs were mainly of the polysulfide type. The mixing was often performed on site. Information on concentrations to be used were not available to the Working Group; however, from a technical point of view, PCB concentrations were likely to be above 5%. Sealants analysed some 40 years after application often contained concentrations of PCBs of 5–15%, with concentrations of up to 35% being reported. The concentration may vary not only between sites, but also within a building. These variations may be the result of use of sealants with different PCB content, or of secondary processes, such as migration out of the matrix. There are reports indicating that inner parts of sealants could contain higher concentrations than the superficial parts (Johansson *et al.*, 2003).

In addition to the use as sealants and flame-retardant coatings, PCBs have also been used in other open applications, such as in inks, adhesives, microencapsulation of dyes for carbonless duplicating paper, conveyor belts, rubber products, paints, pesticide fillers, plasticizers, polyolefin catalyst carriers, immersion oil for microscopes, cutting and lubricating oils, surface coatings, wire insulators, and metal coatings (ATSDR, 2000; Erickson, 2001; Erickson & Kaley, 2011). Also, use in small ballasts for fluorescent lights could be regarded as an open application, especially after long-lasting usage.

(c) Disposal of equipment containing PCBs

Improper handling of electronic waste (e-waste) has been identified as a source of environmental contamination with PCBs, especially for old equipment (Leung *et al.*, 2006). Dismantling of ships has also been identified as a potentially important source of occupational exposure to and environmental contamination with PCBs (Basel Convention, 2003).

With the complete ban on the use of PCBs, stockpiles awaiting elimination have successively appeared in many countries.

In 2000, 23 companies worldwide had facilities for the disposal of equipment containing PCBs, of which 11 were in Europe. The use of solvent for decontamination represents the most common procedure of disposal, followed by destruction by incineration, dechlorination with sodium, retrofilling and vitrification. The most common technology used for destruction of PCBs is by incineration, with an efficiency of between 99% and 99.99999% (IOMC, 1998). For exemple, France has an installed capacity for incineration of PCB residues amounting to around 20 000 tonnes per year (INERIS, 2013).

1.4 Environmental occurrence and exposure

PCBs are found worldwide at measurable levels in all environmental media (soils and sediments, water, air), in wildlife, and also probably in the body of every human. Human exposure to PCBs occurs mostly via ingestion of

contaminated food (see Section 1.4.7), but also via inhalation and dermal absorption.

Soils are natural sinks for persistent and lipophilic compounds such as PCBs; PCBs are absorbed by the organic carbon of the soil, and once absorbed they are relatively persistent (Buckley-Golder, 1999) (see Section 1.4.5). PCBs enter the soil via different pathways: industrial releases from manufacture, use and disposal, accidental releases, atmospheric deposition, application of sewage sludge, and erosion and leachate from nearby contaminated areas. PCBs in organic liquids may be dissolved by soils and then migrate with the solvent.

The congener patterns of PCBs in soils and sediments change over time as a result of the activity of aerobic bacteria (that degrade less chlorinated congeners) and anaerobic bacteria (that can cause partial dechlorination of more highly chlorinated congeners) (Hardell *et al.*, 2010). The patterns found in environmental biota are often referred to as "weathered," since they result from alterations in the composition of a mixture (e.g. resulting from bio accumulative and metabolic processes in higher biological organisms and through bacterial action, exposure to ultraviolet radiation, etc.). "Weathering" processes result in PCB patterns with either a higher chlorinated fraction or congeners with higher bioaccumulative properties compared with the commercial products. "Weathering" must be considered when assessing PCB-associated risks based on studies with experimental animals exposed to commercial PCB products.

Water is a major pathway for migration of PCBs, both in solution and particulate-bound, although PCBs are lipophilic and generally not very soluble in water (see Section 1.4.6). Less chlorinated PCB congeners have greater solubility than more highly chlorinated congeners.

Air is another major pathway for PCB migration (see Sections 1.4.3 and 1.4.4). PCBs are semi-volatile compounds and, as with water solubility, less chlorinated congeners are more volatile than more highly chlorinated ones (Totten *et al.*, 2006). There is extensive evidence that PCBs in aquatic systems exchange with PCBs in air (Bamford *et al.*, 2002). Air transport of PCBs can occur in either the vapour phase or particulate-bound, thus contributing to global pollution and PCB contamination of remote regions of the earth. PCBs in air come from several direct or indirect sources, including industrial facilities, military sites, contaminated bodies of water, landfills and hazardous waste sites, electric arc furnaces, incineration and other forms of combustion, sewage sludge applied to agricultural lands, and construction materials, including in paints (Hu & Hornbuckle, 2010), caulking, light ballasts, floor sealants, and adhesives and plasticizers in older buildings (Wallace *et al.*, 1996).

PCBs from soil, sediment, air and water enter the food-chain by uptake and bioaccumulation in plants and animal fats. There is significant biological magnification of PCB concentration as PCBs move up the food-chain. PCB concentrations vary depending on the degree of bioaccumulation, and are usually highest in carnivorous fish coming from contaminated waters. PCBs are found in the fat of all meat animals, in all dairy products containing fat, and in eggs (ATSDR, 2000; IOM, 2003), sometimes at high concentrations due to local contamination of grasses, and feeding practices in some countries (see Section 1.4.2). Also, it is not uncommon to feed domestic animals with fish meal or oil, or waste animal fats, which results in recycling of PCBs (IOM, 2003). For example, farmed salmon fed with concentrated fish meal or fish oil containing significant amounts of PCBs showed elevated concentrations of PCBs (Hites *et al.*, 2004). PCBs found in food are typically of higher chlorination, since they are less volatile and more biologically persistent in plants and animals than the lower congeners.

Another important route of exposure to PCBs is inhalation; however, it is difficult to determine the relative contribution of inhalation

compared with ingestion. Harrad *et al.* (2006) have suggested that inhalation may account for 4–63% (median, 15%) of overall exposure in humans. PCBs may be attached to indoor dust, which can be either ingested or inhaled. Individuals who spend significant periods of time in the presence of either outdoor or indoor vapour-phase PCBs will have continuous exposure that is not reflected in measurements of "total" PCBs, because the less chlorinated congeners are more rapidly metabolized and excreted by the human body (Fig. 1.5; Johansson *et al.*, 2003). Concentrations of different PCB congeners were measured in blood from individuals living in houses where PCB-containing sealant was used. Concentrations of most congeners were only slightly elevated (1.2 to 3.2 times), but the two congeners with a low level of chlorination (PCB-28 and PCB-66) were detected at much higher concentrations (30 and 9 times, respectively) in contaminated flats than in control flats.

Dermal absorption of PCBs may occur primarily in the occupational setting, but also through contact with contaminated sediments or other applications to the skin (Wester *et al.*, 1987, 1993). Less chlorinated congeners are more rapidly absorbed through the skin than more highly chlorinated congeners (Garner & Matthews, 1998).

Congener patterns in the general human population are always different from any pattern found in commercial PCB products (Patterson *et al.*, 2009). The factors that may explain this are:

- The general public is exposed to multiple sources of PCBs, only rarely to a single commercial product.
- There may be more than one route of exposure for almost all matrices/animals/humans.
- Dechlorination occurs to varying degrees in sediments, soils, water and air. Commercial PCB products will volatize to some degree, and in doing so, will lose less chlorinated congeners.
- PCBs ingested by fish and animals will be metabolized (to less chlorinated and hydroxylated congeners) to different degrees. Thus most food stuffs will demonstrate a shift in the congener profile compared to the commercial product.
- When inhalation is the major route of exposure, there is selective exposure to the more volatile, less chlorinated and less persistent congeners.
- Genetic differences among individuals may confer differences in metabolic activity and selective metabolism of different congeners.

1.4.1 Diffuse sources of PCBs worldwide

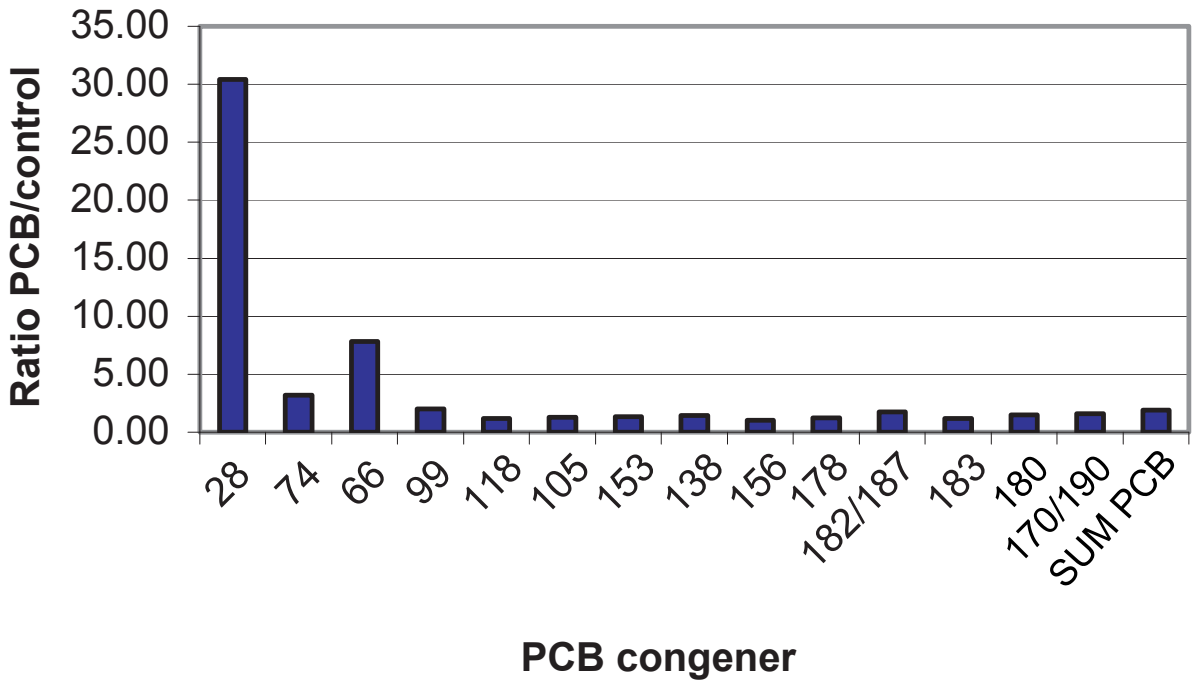
(a) North America

The two Monsanto facilities that manufactured PCBs in the USA were located in Anniston, Alabama, and Sauget, Illinois. In Anniston, more than 400 000 tonnes of PCBs were produced, at least 4550 tonnes were discarded in two landfills, and at least 20.5 tonnes were released into the atmosphere (Hermanson & Johnson, 2007). Many of the large industries using PCBs manufactured by Monsanto were located near major bodies of water, and PCBs were released into the environment as a result of unintentional leaks, volatilization during the production process, and migration from associated landfills and waste products. There was also production, at lower quantities, by Geneva Industries in Houston, Texas (de Voogt & Brinkman, 1989). As a result, contamination has occurred in many rivers and streams near these sites of production (see Section 1.4.6(a)).

(b) Europe

In western Europe, many chemical plants are located along major rivers (i.e. Rhine, Rhone, and Seine) and there have been several isolated incidents of organic chemical pollution. The Seine estuary remains one of the most polluted

Fig. 1.5 Blood PCB concentrations in individuals living in PCB-contaminated flats relative to individuals living in control flats



PCB, polychlorinated biphenyl
From Johansson et al. (2003)

in Europe (RNO, 2012). Also, the Venice lagoon in Italy is particularly polluted owing to the proximity of an important industrial district (the Marghera Harbour) (see Section 1.4.6(b)).

In the Slovak Republic, the Chemko Chemical Co. (based in the Michalovce district) produced 21 000 tonnes of commercial PCB mixtures between 1959 and 1984 (Delor 103, 104, 105, 106, Delotherm DK and DH, Hydelor 137). Improper disposal from the Chemko plant via release of effluent directly into the Laborec river resulted in long-term environmental contamination.

During the conflict of the former state union of Serbia and Montenegro throughout the 1990s, the burning or damaging of industrial and military targets resulted in the release of large amounts of PCBs into the environment: more than 1000 electro-transformer stations that contained PCB oil were damaged. After the bombardment of Kragujevac, Serbia, 2500 kg of PCB-based oil from the transformers of the Zastava automobile industry were spilled.

A French inventory reported that the number of installed transformers containing at least 100 kg of PCBs was 100 000 units in 1987, corresponding to 50 000 tonnes of fluids containing 60% PCBs (Pyralene), and to 50 000 tonnes of carcasses with 5% of PCB residues. The 250 000 medium-voltage capacitors represented about 3000–5000 tonnes of pure PCBs, while the low-voltage capacitors represented 1500–2000 tonnes of hardly extractable PCBs.

In Spain, an inventory in 1997 reported some 6000 tonnes of PCBs, although the amount of material containing or contaminated with PCBs could reach 200 000 tonnes.

(c) Asia

Contamination of soil and sediments has been reported in the Russian Federation, China, Viet Nam, and Japan. Such contamination may originate from PCB producing plants (e.g. China, Japan, Democratic People's Republic of Korea), or from e-waste recycling facilities (e.g. China). In addition, two major accidents of food contamination occurred in Taiwan, China and Japan (see Section 1.4.2(a)).

(d) South and Central America

There has been no manufacture of PCBs in South and Central America, but there has been widespread use of PCB-containing transformers and other PCB-containing devices.

(e) Africa

There has been no manufacture of PCBs in Africa, but there has been widespread use of PCB-containing transformers and other PCB-containing devices. In Africa, several studies showed an increase in the number of sources of PCBs, due to leakage and wrongly disposed transformers, shipwrecks, and biomass burning.

Another major source of exposure is the importing of e-waste and increase of e-waste recycling facilities, usually illegal, but common in Ghana, Senegal, Nigeria, Kenya, and the United Republic of Tanzania. A report by the United Nations Environment Programme (UNEP) documented issues concerning e-waste in South Africa, Kenya, Uganda, Morocco, and Senegal (UNEP, 2009).

In spite of the lack of homogenous data, an attempt has been made to compare the main PCB stocks that reside in the various countries of the region. [These data should only be seen on the relative scale since lacking the accuracy to make them valuable in the absolute sense.]

In Algeria, the national inventory of electrical equipment and PCB wastes identified 6770 appliances and around 4000 tonnes of oil to remove. The deposit of transformers, capacitors and various equipment containing PCBs was estimated at 1700 tonnes in Tunisia and 1150 tonnes in Morocco (Business Med, 2010).

1.4.2 Accidental releases into the food-chain

(a) Asia

Cooking oil contaminated by Kanechlor has been the source of two accidental mass poisonings in western Japan (later called "Yusho," oil disease in Japanese) and in Taiwan, China (later called "Yucheng," oil disease in Chinese). Commercial PCB mixtures were used as heat-transfer media in oil tanks; leakage of the pipes caused exposure to the PCB mixture and PCB pyrolytic products, mainly PCDFs and polychlorinated quaterphenyls (PCQs) (Masuda *et al.*, 1986). Patients from both countries have been exposed to comparable quantities of PCBs and PCDFs. The PCB/PCDF concentrations in the Yusho oil were higher (several hundred ppm to 3000 ppm) than those in the Yucheng oil (53 to 100 ppm) (Guo *et al.*, 2003); however, on average, Yucheng patients consumed the contaminated oil for a longer duration than the Yusho patients.

(i) Yusho incident, Japan

In 1968, the Yusho incident involved approximately 1800 people who ingested rice oil contaminated by Kanechlor 400 and its pyrolytic products, mainly in Fukuoka and Nagasaki prefectures (Masuda, 1994a, b; Kuratsune, 1996; Matsueda *et al.*, 1993; Todaka *et al.*, 2007a; Nagayama *et al.*, 1977; Tanabe *et al.*, 1989; Masuda *et al.*, 1998; Ohta *et al.*, 2008a). Affected people developed a "strange skin disease," including acne-form eruption, follicular accentuation, and pigmentation, as well as eye discharge and swelling of eyelids. The mean concentrations of seven PCB congeners (PCB-105, PCB-118, PCB-138, PCB-153, PCB-157, PCB-170, and PCB-180) detected in blood were 6.7 ppb and 3.84 ppb (95% confidence

interval, 3.54–4.17), 5 and 20 years after being exposed, respectively (Masuda & Yoshimura, 1982). Mortality data among registered Yusho patients were identified by follow-up studies to 1990 and 2007. The first of these two reports (Ikeda & Yoshimura, 1996) reported serum PCB concentrations in the range of 0 to 35 ppb in 1972, and a decrease to about 5 ppb in 1984 (Iida *et al.*, 1999) (see Sections 1.4.9(b)(iii) and (c)(iv) for additional data on PCB concentrations in blood and adipose tissue, respectively).

(ii) Yucheng incident, Taiwan, China

In 1978–9, the Yucheng incident involved approximately 2000 people who ingested rice oil contaminated with Kanechlor 500 and its pyrolytic products (Hsu *et al.*, 1985). After a few months, these people developed chloracne, hyperpigmentation, severe fatigue, peripheral neuropathy, and other signs and symptoms similar to Yusho disease. On the basis of a dietary questionnaire, it was estimated that Yucheng patients had consumed on average about 1 g (range, 0.7–1.4) of PCBs and 3.8 mg (range, 1.8–5.6) of PCDFs (Lan *et al.*, 1981). Another study estimated the intakes of PCBs, PCDFs, and PCQs by Yucheng patients at 673, 3.8, and 490 mg, respectively (Masuda *et al.*, 1986). DL-PCBs contributed to approximately 30% and 20% of the total TEQ (toxic equivalent) in Yucheng men and women, respectively. Compared with the general population in Taiwan, China, the mean total serum PCB concentrations in the Yucheng victims were still nine times higher 15 years after exposure (see Sections 1.4.9(b)(iii) and (c)(iv) for additional data on PCB concentrations in blood and adipose tissue, respectively).

(b) Europe

In Europe, the "Belgian dioxin crisis" was caused by the accidental release of 50 kg of a commercial PCB mixture contaminated with 1 g of dioxins commonly found in transformers, to a stock of recycled fat used for the production of 500 tonnes of animal feed. In May 1999, it appeared that more than 2500 poultry and pig farms could have been contaminated. Chickens showed the classical signs of oedema disease.

In Ireland in 2008, a tank for storage of pork fat was contaminated with heat-transfer fluid containing PCBs (Hovander *et al.*, 2006). [The Working Group noted that the label of "dioxin crisis" attributed to these episodes of PCB feed contamination was inappropriate.]

1.4.3 Outdoor air

PCBs in outdoor air may be a significant source of exposure. Concentrations of PCBs in air depend on a variety of factors, including temperature and proximity to local sources. Temperature is particularly important in controlling the cycle of volatilization and precipitation. Proximity to local sources, such as industrial facilities, landfills, or contaminated bodies of water, results in elevated air concentrations of both vapour phase and particulate-bound PCBs that dissipate with distance at different rates, resulting in both local and distant contamination. Combustion and other high-temperature processes generate PCBs, in particular during combustion of highly chlorinated compounds; however, this route of unintentional formation is considered to contribute little to total airborne PCBs. Migration to the outdoor environment has also been shown to occur as a result of erosion of exposed sealants.

(a) North America

PCB concentrations in outdoor air vary greatly between urban and rural sites in North America, and may be very high near industrial facilities and other contaminated sites (Table 1.16). These differences reflect primarily the impact of local sources and dilution in air, but also the deposition of PCBs at lower temperatures.

The major sources in Chicago are from landfills, sewage sludge drying beds, and transformer storage yards (Hsu *et al.*, 2003). Shen *et al.*

Table 1.16 PCB concentrations in outdoor air in North America

Reference	Location, sources	PCBs measured	PCB concentration in pg/m³ as mean and/or range	Comments
Vorhees *et al.* (1997)	Near a PCB-contaminated site, New Bedford Harbor, Massachusetts	"PCB concentrations"	400–61 000	
	Comparison neighbourhood		100–8200	
Hung *et al.* (2001)	Canadian Arctic	Sum of 102 congeners	28 in 1993; 23 in 1997	PCB-28, PCB-52, and PCB-118 showed little or no decline over time
Hermanson *et al.* (2003)	Near the former Monsanto PCB-manufacturing facility in Anniston, Alabama	Sum of 120 congeners	8700–82 000 [annual average, 27 000]	
Totten *et al.* (2004)	Urban sites (Camden and Jersey City, New Jersey)	Sum of 116 congeners	Average, 3250 and 1260, respectively	
	Remote and suburban areas at various sites near the New York City metropolitan region		Averages of 150–220	
Sun *et al.* (2006)	Six sites near near USA–Canadian Great Lakes (Lake Michigan near Chicago)	Sum of 84 congeners	± 100–1400	
Hermanson & Johnson (2007)	Near the former Monsanto PCB-manufacturing facility in Anniston, Alabama	PCBs in tree bark	171 927 ng/g (ppb) lipid near the site, to 35 ng/g (ppb) lipid at a distance of 7 km	Tree bark serves as passive vapour-phase air sampler
Sun *et al.* (2007)	Six sites distant from urban areas near USA–Canadian Great Lakes (Lakes Superior and Huron)	Sum of 84 congeners	60–86	
	Six sites near near USA–Canadian Great Lakes (Lake Erie)		± 1.1–230	
Palmer *et al.* (2008)	Near the contaminated Hudson River, downstream communities	Sum of 84 congeners	Median, 711	Concentrations were higher closer to the river than further away, and higher in warmer than cooler months of the year. The congener pattern in air was primarily PCBs with three or four chlorines
	City upstream of the industrial sites that caused the contamination		Median, 431	
Palmer *et al.* (2008)	Contaminated portion of the Hudson River	Sum of 84 congeners	102–4011 (median, 711)	
	Community upstream of the contamination		80–2366	
Harrad *et al.* (2009)	Toronto, Canada	Sum of 8 congeners	100–1400 (mean, 350)	
Li *et al.* (2010)	North America	Sum of PCBs	79 (49–120)	
	Remote sites in Alaska and rural sites in the lower 48 states of the USA		1–50	
	Large urban areas like Chicago		1000 and 150 000	
Persoon *et al.* (2010)	Cleveland, Ohio	Sum of 151 congeners	1730–4240	
	Chicago, Illinois		1130–2690	

PCB, polychlorinated biphenyl

(2006) found large relative differences in air PCB concentrations between urban, rural and remote sites, with the highest concentrations in Toronto, Canada, and the Eastern third of the USA [absolute concentrations could not be quantified] using results from passive air samplers in 31 stations in Canada and the USA.

(b) Europe

In Europe, the reported PCB concentrations in outdoor air range from ~10 up to ~1000 pg/m^3 in western European countries and from ~50 up to ~9000 pg/m^3 in eastern European contries.

Measurement in the Baltic region showed PCB concentrations in southern Norway to be rather high and similar to those in urban areas (Backe *et al.*, 2000; Agrell *et al.*, 2001). Results from the Czech national monitoring system and European Monitoring and Evaluation Programme (EMEP) background monitoring stations also showed relatively high PCB concentrations in this country (EC, 2004). Typical values for background sites usually range up to ~100 pg/m^3 and up to several 100s pg/m^3 for contaminated areas (Kocan, 2000, 2001).

PCB concentrations in outdoor air may also be measured in precipitation as total deposition rates (ng/m^2 per day). In southern Sweden (Backe *et al.*, 2002), PCB concentrations ranged from 1.18 to 81.4 ng/L, with no seasonal trends. In Paris, France, average PCB concentrations (sum of seven congeners) in rain during 1986–2001 remained approximately constant at about 40 ng/L (Chevreuil *et al.*, 2001).

Declining concentrations of PCBs have been observed since the early 1960s and 1970s, decreasing by 67% in France (EC, 2004) and by 78% in the United Kingdom (CITEPA, 2013) over 20 years. The difference observed between the steady concentrations in rain and the decrease in general atmospheric emissions may be partly explained by water solubility limits and differences between point sources and global emissions.

Air concentrations of the seven indicator PCBs 28, 52, 101, 118, 153, 138 and 180 were measured at four locations in the Czech Republic, Finland, Sweden, and the Netherlands, from 1996 to 2001. Measured values did not vary noticeably during this period at any location (Fig. 1.6). This suggests that a steady-state has been reached between degradation and environmental cycling, with an ongoing low-level input from existing equipment and contaminated material (Holoubek *et al.*, 2003).

(c) Asia

Limited information on the concentrations of PCBs in air and dust has been reported in Asian countries (Table 1.17). One of the most extensive studies reported results for outdoor air samples from 55 sites in Japan, 20 in China, 30 in the Republic of Korea, and 1 in Taiwan, China. The range of concentrations was 100–1000 pg/m^3.

(d) South and Central America

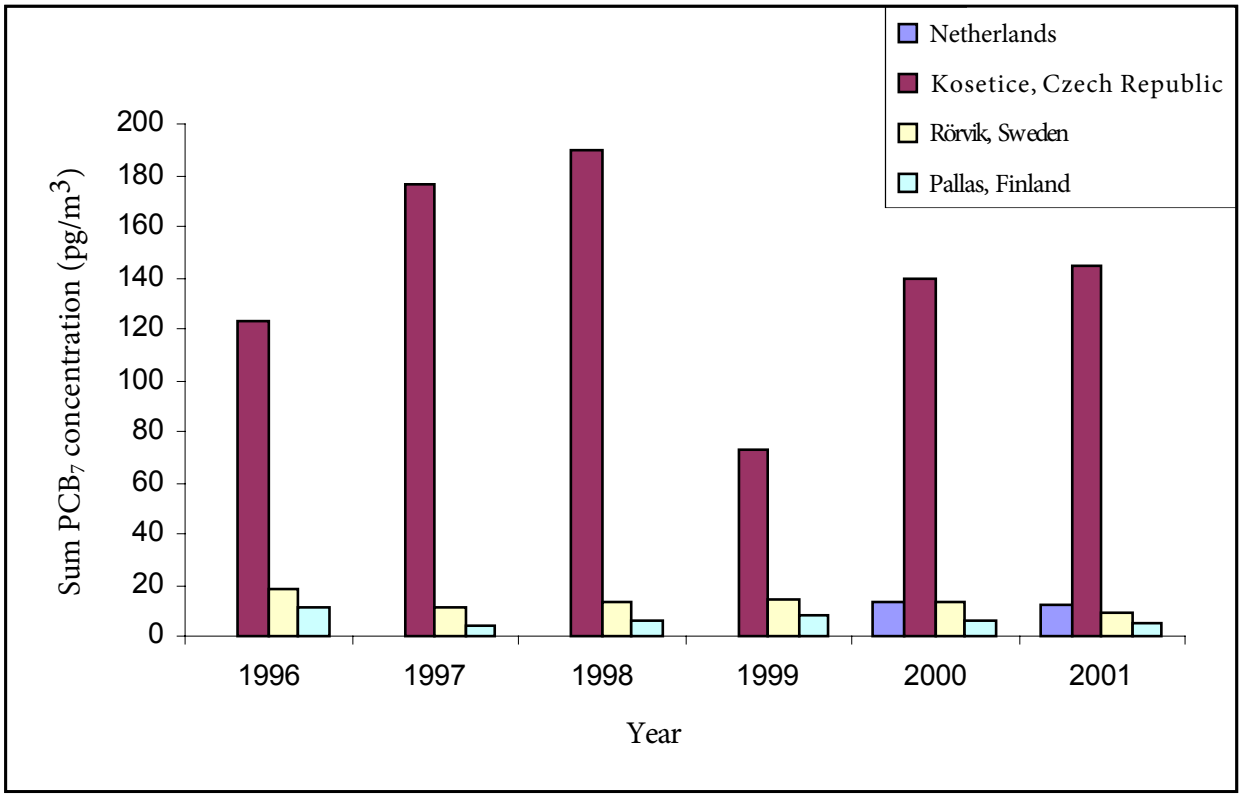
Shen *et al.* (2006) found large relative differences in air PCB concentrations between urban, rural and remote sites using passive air samplers in 4 stations in Mexico, Belize, and Costa Rica. One site in Mexico had higher concentrations than sites in Central America and in Canada.

Li *et al.* (2010) reviewed information from various research groups around the world and reported the average concentration of the sum of PCBs in air to be 66 pg/m^3 (range, 9–670 pg/m^3) for South America, and 59 pg/m^3 (range, 17–150 pg/m^3) for Central America.

(e) Africa

Only recently have data from passive air samplers deployed on the African continent become available. PCB concentrations have been reported as very high in Senegal (500 pg/m^3) (Klánová *et al.*, 2009), Côte d'Ivoire, and the Gambia (up to 300 pg/m^3) (Gioia *et al.*, 2011). Concentrations in some areas in South Africa, Kenya, Egypt, the Democratic Republic of the

Fig. 1.6 Annual average atmospheric concentrations of seven indicator PCBs (PCB_7) from four European Monitoring and Evaluation Programme stations in Europe, 1996–2001



PCB_7, sum concentration of PCB-28, PCB-52, PCB-101, PCB-118, PCB-153, PCB-138, and PCB-180
From Holoubek *et al.* (2003)

Congo, Ghana, Mali, and the Sudan were also high, and comparable to those in urban areas in more developed countries. These levels could not be explained by biomass burning or primary emissions, and were probably due to e-waste dumps. Lower concentrations have been measured in the Congo, Ethiopia, Mauritius, Nigeria, the Togolese Republic, Tunisia, and Zambia.

(f) Vegetation used for monitoring studies

Plant foliage is a reliable proxy for monitoring levels of vapour-phase compounds in outdoor air since it bioaccumulates organic pollutants. Several researchers have used vegetation, grass, conifer needles, mosses, pollen, and leafy vegetable species (cabbage and lettuce) as biomonitors to evaluate patterns of PCB contamination (Larsen *et al.*, 1985; Reischl *et al.*, 1989; Kylin, 1994; Simonich & Hites, 1995). This method has been employed in high-mountain ecosystems (Daly & Wania, 2005), and in several countries, including the Czech Republic (Holoubek *et al.*, 1994), Poland (Migaszewski, 1999), western Finland (Sinkkonen *et al.*, 1995), Germany (Reischl *et al.*, 1987), Italy (Gaggi *et al.*, 1985), and France (Granier & Chevreuil, 1992).

1.4.4 Indoor air

PCBs have been shown to migrate into surrounding materials, such as concrete or wood, and to indoor air. The major sources are PCB-containing caulk, paint (where PCB-11 is the main marker), floor sealants, and ballasts

Table 1.17 PCB concentrations in outdoor air and dust in Asian countries

Reference	Country, region Date of study	Sources	PCBs measured Comments	Concentrations
Iwata *et al.* (1995)	Russian Federation, Lake Baikal May 1992	Six outdoor air samples from research vessel	Kanechlors 300, 400, 500, 600 as standards	Range, 8.7–23 pg/L
McConnell *et al.* (1996)	Russian Federation, Lake Baikal June 1991	A total of 19 outdoor air samples	Aroclors 1242 and 1254 as standards	Mean, 196 ± 65 pg/m^3
Hogarh *et al.* (2012)	Taiwan, China; China; Japan; Republic of Korea March–May, 2008	Outdoor air samples from 55 sites in Japan (37 rural, 4 suburban and 14 urban), 20 in China (3 rural and 17 urban), 30 in the Republic of Korea (12 rural, 2 suburban and 16 urban), and 1 in Taiwan, China	Sum of 202 congeners	Japan, 40–760 pg/m^3 China, 300–2500 pg/m^3 Taiwan, China, about 317 pg/m^3 Republic of Korea, 36–600 pg/m^3
Thacker *et al.* (2013)	India, central and western regions 2009–2010	Outdoor air samples from various cities	Sum of dioxin-like PCBs	Range, 0.0001 × 10^{-1} to 0.0295 ng TEQ/Nm^3

PCB, polychlorinated biphenyl; TEQ, toxic equivalent

in lighting devices. Outgassing from contaminated dust may also contribute. Joint sealants are increasingly recognized as important diffuse sources of indoor air contamination by PCBs.

(a) North America

PCBs have been measured in indoor air in several studies (Vorhees *et al.*, 1997; Vorhees *et al.*, 1999; Herrick *et al.*, 2004; Colt *et al.*, 2005; Franzblau *et al.*, 2009; Harrad *et al.*, 2009). In the USA it was reported that indoor air concentrations of PCBs were 5–300 times greater than those in outdoor air (Wallace *et al.*, 1996), and that concentrations were higher in older buildings. The concentrations of PCBs in indoor air in North America are summarized in Table 1.18.

(b) Europe

The highest indoor concentrations (up to 7500 ng/m^3) have been reported in buildings constructed between 1960 and 1975 from prefabricated concrete elements sealed with elastic materials containing PCBs (Balfanz *et al.*, 1993). Joint sealants containing PCB were discovered in various public buildings in Europe (Kohler *et al.*, 2005; Wilkins *et al.*, 2002). Estimated indoor PCB concentrations in contaminated sections were the lowest in microenvironments such as cars (8.92 ng/m^3), and were inversely related to the degree of chlorination of the PCB mixtures used (Hammar 1992; Harrad *et al.*, 2006; Kuusisto *et al.*, 2006, 2007; Frederiksen *et al.*, 2012). The concentrations of PCBs in indoor air in Europe are summarized in Table 1.19.

(c) Asia

Indoor floor dust samples (n = 43) collected from rural homes and mosques in Gujarat, Pakistan, showed median total PCB concentrations of 0.67 ng/g (range, 0.3–6.1 ng/g) (Ali *et al.*, 2012). The PCB profile was dominated by PCB-153 (> 60% of the sum of PCBs), with concentrations between < 0.2 and 2.4 ng/g. These PCB concentrations were 10 times lower than those reported in house dust in Singapore (Tan *et al.*, 2007).

1.4.5 Soil and sediments

PCBs can enter soil and sediments through various routes. Sediments constitute an important sink for PCBs entering the marine environment. Sewage sludges are monitored for PCBs in countries where they are largely used (60%) in agriculture. The dumping of incinerator-related materials and/or the inadequate management of commercial PCBs have resulted in significantly elevated PCB concentrations.

1.4.6 Water

Inputs of PCBs to the hydrological cycle are principally via discharges of sewage and industrial effluents, urban run-off, leachates from solid waste landfill sites, atmospheric deposition and, of increasing concern, via agricultural run-off (Scrimshaw *et al.*, 1996).

Water can contain PCBs either in solution or bound to particulates. While PCBs are not very water-soluble, water can be a significant source of exposure to less chlorinated congeners that have a greater solubility than more highly chlorinated congeners. PCB concentrations in sea and freshwater are summarized in Table 1.20.

(a) North America

(i) Drinking-water

In the USA, the EPA has set a goal for PCBs in drinking-water of zero, and a maximum contaminant concentration of 500 ng/L (500 ppt), with sources being primarily landfills, and discharge of waste chemicals (EPA, 2014). While conventional treatment of drinking-water will remove particulate-bound PCBs, those that are soluble are often not completely removed. Solubilities of individual PCB congeners vary from about 4 ppm for monochlorobiphenyl to as low as 0.0007

Table 1.18 PCB concentrations in indoor air in North America

Reference	Location	Source	PCBs measured	Concentration	Comments
Vorhees *et al.* (1997)	New Bedford Harbor, Massachusetts, USA	18 homes	Sum of 65 congeners	Geometric mean concentration, 18 ng/m³ (range, 7.9–61 ng/m³)	
		Comparison neighbourhood		Geometric mean concentration, 10 ng/m³ (range, 5.2–51 ng/m³)	
Vorhees *et al.* (1999)	New Bedford Harbor, Massachusetts, USA	House dust in homes surrounding the Superfund site	Sum of 65 congeners	1400 (range, 320–23 000) ng/g dry weight	
		Comparison neighbourhood		60 (15–290) ng/g	
Herrick *et al.* (2004)	Greater Boston, USA	24 university buildings		> 36 200 ppm 111–395 ng/m³	One third of the 24 buildings investigated contained caulk at concentrations > 50 ppm (the EPA limit)
Colt *et al.* (2005)	Four geographical regions in the USA	PCBs in carpet dust, 443 homes of Caucasian Americans who served as controls in a case–control study on non-Hodgkin lymphoma		Specific concentrations not reported	PCB concentration in dust was significantly related to age of the house, being greatest in homes built before 1940, and significantly greater in homes built in 1960–1979 (when PCBs were being manufactured in the USA) than in homes constructed after 1980
Franzblau *et al.* (2009)	Five counties in Michigan, USA	House dust House dust	PCB-123 PCB-118	439 000 ppt 33 600 000 ppt	Dioxin-like PCBs contributed 66.2% of the total WHO TEQ found in dust
Harrad *et al.* (2009)	Texas, USA	20 homes	Sum of 9 tri- to heptachlorinated congeners	200 ng/g (ppb); (range, 0.71–620 ng/g)	
	Toronto, Ontario, Canada	10 homes	Sum of 9 tri- to heptachlorinated congeners	260 ng/g (ppb) (range, 51–820 ng/g)	Levels were more than four times higher than those measured in cities in the United Kingdom and New Zealand

EPA, United States Environmental Protection Agency; PCB, polychlorinated biphenyl

Table 1.19 PCB concentrations in indoor air in Europe

Reference	Country	Source	PCB concentration (mean or range)	Comments
Hammar (1992)	Sweden	Joint sealants	80 ng/m^3	Outside the building, mean concentrations were 0.5–4.6 ng/m^3
Balfanz *et al.* (1993)	Germany	Air from contaminated buildings	Range, > 300–7500 ng/m^3	Indoor PCB concentrations were inversely related to the degree of chlorination of the PCB mixtures used
Wilkins *et al.* (2002)	Denmark (Organization of Sealant Branch's Manufacturers and Distributors)	Dust from public and residential buildings with excessive microbial growth	Estimated inventory of 75 tonnes in caulking materials	Concentration in polluted buildings was 10–20 times higher than the amount found in samples from other buildings
Kohler *et al.* (2005)	Switzerland	Joint sealants in public buildings	> 10 g/kg in 48% of samples	70% of samples contained PCB mixtures such as Clophen A50, Aroclor 1248, and Aroclor 1254
Harrad *et al.* (2006)	United Kingdom	Homes, offices, cars, public microenvironments	8.92 ng/m^3	The least contaminated microenvironment was the car (average, 1391 pg/m^3)
Kuusisto *et al.* (2007)	Finland	Walls/floor	110–540 µg/m^2	Detected PCBs were highly chlorinated
Frederiksen, *et al.* (2012)	Denmark	Air from uncontaminated apartments Elastic sealants from contaminated apartments	168–3843 ng/m^3 187–221 680 mg/kg	Significant correlations were observed between the lower chlorinated congeners in air and sealant

PCB, polychlorinated biphenyl

Table 1.20 PCB concentrations in various types of water around the world

Reference	Type of water	Location	PCB measured	Concentration	Comments
North America					
Jeremiason *et al.* (1994)	Lake	Lake Superior, USA		2.4 ng/L in 1980; 0.18 ng/L in 1992	
Connolly *et al.* (2000)	River	Hudson River		Sometimes > 1300 ng/L	Varied greatly with season and water flow
Rowe *et al.* (2007)	River	Delaware River	Sum of 116 congeners	420–1650 pg/L	
Wang *et al.* (2012)	River	Mississippi River	Sum of 27 congeners	86 and 254 ng/L	
	Lake	Lake Pontchartrain		134–728 ng/L	In some months the PCBs in river water were primarily in the liquid phase, whereas in other months primarily in the sediment
South and Central America					
Rissato *et al.* (2006)	River	Sao Paulo State, Brazil	Sum of seven congeners	0.02–0.5 ng/L	Predominantly lower chlorinated congeners
Africa					
Scarpato *et al.* (2010)	Sea	Tunisia Morocco–Algeria coastal sites	Sum of 10 congeners	10–12 ng/g 7–8 ng/g	PCB contamination evaluated by mussel-caging technique (exposure, 12 weeks)
Jayed *et al.* (2010)	Ocean	Thirteen sites along the Atlantic Moroccan coast	Sum of PCB-28, PCB-153, PCB-138	Wet season: 11 ng/g Dry season: 8.2 ng/g	Concentrations in mussels during wet and dry seasons not significantly different, but values in the northern sites exceeded 2–3 times the medians registered for the other sampling sites
Vorkamp *et al.* (2010)	Ocean	Cape Town harbour Cape Town sea shore Ghana coast	Sum of congeners	81 ng/g dw 15 ng/g dw 5 ng/g dw	Bivalve samples
Europe					
Nondek & Frolikova (1991)	Lake	Sumava lakes, Czech Republic		1900 ng/g	Contamination due to atmospheric transport to non-industrialized areas
Winkels *et al.* (1998)	River	River Danube, Czech Republic		< 5 ng/g dw	Contamination due to flood disaster in the Moravian part of the Czech Republic in July 1997

Table 1.20 (continued)

Reference	Type of water	Location	PCB measured	Concentration	Comments
Fillmann *et al.* (2002)			Sum of seven congeners	≤ 700 ng/g dw (2–196 µg/kg ww in fish)	
UNEP (2002)	River	Krupa, Sana and Lepenica rivers, Balkan area, Slovenia		380 ng/L (in 1988) 100 ng/L (in 1997)	The factory in Semič was storing 5–6 tonnes of waste oil containing PCBs
Desmet *et al.* (2012)	River	Rhone river, France	Sum of PCB_7	1–40 ng/g dw	Concentrations consistently lower than those found during the previous decade (Burns & Villeneuve, 1987). Maximum PCB concentration was identified in 1960–75. The downward trends in concentration followed emission reductions, although soil concentrations decreased at much slower rates (Tolosa *et al.*, 1995)
ADEME (1998), Blanchard *et al.* (2001)	Wastewater	Wastewater treatment plants, France	Sum of seven congeners	Input water, 100–300 ng/L Output water, 15–54 ng/L	In 1999, average concentration was 15–26 ng/L. High levels of DL-PCBs in eel from Dutch freshwater were reported in a screening of Dutch fishery products (Van Leeuwen *et al.*, 2002)
Asia					
Kucklick *et al.* (1994)	Lake	Lake Baikal, Siberia, the Russian Federation, June 1991	61 PCB congeners using standards of Aroclor 1242, 1254, and 1260	Mean, 560 ± 180 pg/L for dissolved phase, and 420 ± 400 pg/L for particulate phase	
Iwata *et al.* (1995) May 1992	Lake	Lake Baikal, the Russian Federation, June 1991	Kanechlors 300, 400, 500, 600 as standards	Range, 8.7–23 pg/m^3	
McConnell *et al.* (1996) June 1991	Lake	Lake Baikal, the Russian Federation, June 1991	Aroclors 1242, 1254 as standards	Mean, 1 324 ± 96 pg/m^3	

DL-PCB, dioxin-like polychlorinated biphenyl; dw, dry weight; PCB, polychlorinated biphenyl; ww, wet weight

ppm for the decachlorobiphenyl (Erickson, 1997). Thus under certain circumstances, drinking-water can still be a source of exposure to less chlorinated congeners.

(ii) Sea and freshwater

The USA–Canadian Great Lakes are contaminated by multiple sources of PCBs (Bhavsar *et al.*, 2007; Turyk *et al.*, 2012). It has been shown that industrial sites on rivers feeding Lake Erie received the largest quantities of PCBs, with 26% derived from atmospheric deposition (Kelly *et al.*, 1991). The Hudson River in New York is highly contaminated with PCBs because of releases from two large capacitor plants (Carpenter & Welfinger-Smith, 2011), the Fox River in Wisconsin is highly contaminated because of releases from a manufacturer of carbonless copy paper, and a paper mill (Imamoglu *et al.*, 2004), and the St Lawrence River and several of its tributaries have been contaminated by releases from aluminium foundries operated by companies that discarded hydraulic fluids containing PCBs in drains (Fitzgerald *et al.*, 1996). The Hudson and Fox Rivers are being dredged to remove these contaminants.

(b) Europe

(i) Sea

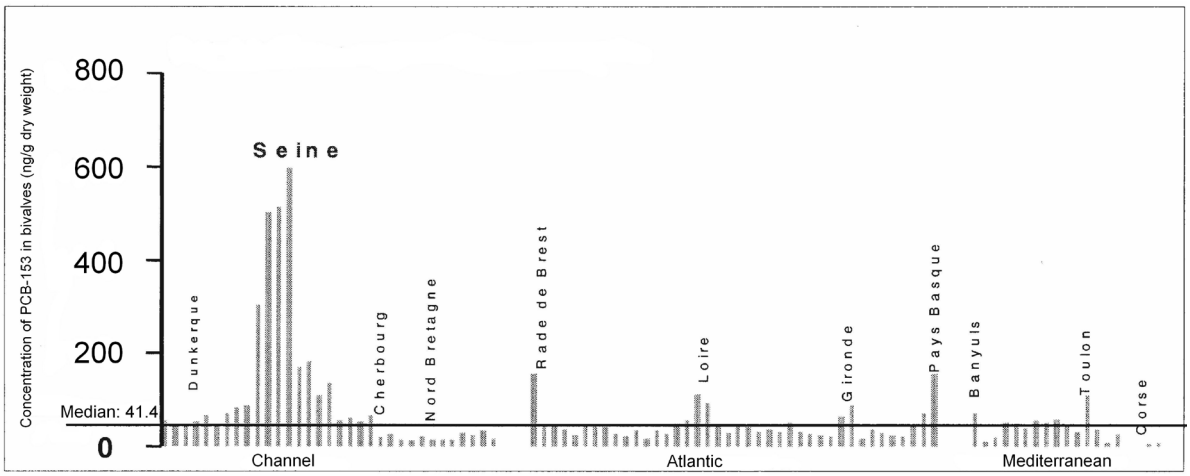
An extensive review of data obtained during the 1980s has been published (Tolosa *et al.*, 1995). In general, the concentrations of PCBs for all the investigated areas in the Mediterranean Sea were similar except in the Ligurian Sea where concentrations were higher. Predictably, the highest concentrations were reported in urban and industrial wastewaters (e.g. from Marseille and Barcelona) as well as in river discharges (e.g. from the Rhone), and decreasing concentration gradients have been found in transects offshore from these sources. PCB concentrations in the suspended particulate matter from coastal and open Western Mediterranean waters were of 5–35 pg/L in 1990, of the same order of magnitude as those reported in other regions, e.g. North Sea and North Atlantic. A more recent study covering the whole Western basin also shows a spatial gradient from the continental shelf (3.5–26.6 pg/L) towards the open sea (1.7–6.6 pg/L); a relatively important enrichment (8.4 pg/L) in open sea stations located in higher productivity frontal zones was observed (Dachs *et al.*, 1997). The dissolved PCBs (Σ12 congeners) amounted to 28–63 pg/L. Total concentrations of PCBs in estuarine and coastal sediment samples of the Mediterranean Sea ranged from 0.04 to 1684 ng/g dw (Koci, 1998; Vale *et al.*, 2002; Vojinovic-Miloradov *et al.*, 2002; Cardellicchio *et al.*, 2007).

During 1974–82, PCB concentrations decreased by a factor of 3 in offshore Monaco (Burns & Villeneuve, 1987), while the surface sediments of the Adriatic coast did not show a temporal trend (Picer & Picer, 1991).

Concentrations of PCBs in ocean water are usually in the low picogram per litre range. The general trend for concentrations in the Baltic Proper suggests an increase in PCB concentrations from the early 1970s onwards (ICES, 2000). This is an opposing trend to the decreasing concentration trends for PCBs in biota from the Baltic Proper (HELCOM, 1996; Roots, 1996).

The monitoring of PCBs in coastal areas may be based on measurements in mussels. Trends in PCB concentrations in the Seine estuary in France are reported in Fig. 1.7 (RNO, 2012). The rate of decrease was 3.5% per year. As reported by the Arctic Monitoring and Assessment Programme (AMAP), several time-series of PCB-153 concentrations in blue mussels from around Iceland showed significant decreasing trends; however, one time-series from a fjord system showed a significant increase (Rigét *et al.*, 2010). Active mussel watching (mussel transplantation) has also been applied in monitoring programmes in Africa (see Table 1.20).

Fig. 1.7 PCB contamination along the coast of France



Concentrations of PCB-153 in mussels or oysters (used as "sentinel species") sampled from coastal areas of France. The Seine estuary and bay are heavily exposed to manmade chemicals of terrestrial origin derived from the urbanized and industrialized river Seine.
Data from The French pollution monitoring programme (Réseau National d'Observation de la qualité du milieu marin)
Reproduced from Abarnou *et al.* (2002), with permission from the publisher

(ii) Freshwater

The major source of freshwater contamination in Europe comes from diffuse leaching of products from users, households, and industries into wastewater streams (UNEP, 2002). The areas most polluted by flood disasters are in Poland (the River Odra) (Wolska *et al.*, 1999; Protasowicki *et al.*, 1999) and in the Czech Republic. The River Danube is a major source of contamination to the Black Sea; however, many chlorinated hydrocarbons have been banned by several European and other countries in the past 10 years (Winkels *et al.*, 1998; Covaci *et al.*, 2002c; Fillmann *et al.*, 2002; see Table 1.20).

Industrial contamination is known to have occurred in Germany (the Rivers Elbe and Rhine and their tributaries) (Brauch, 1993), in former Czechoslovakia (the Sumava Lakes) (Nondek & Frolikova, 1991), in England and Ireland (where however approximately a 50% decline in concentrations between 1970 and 1990, was recorded) (Sanders *et al.*, 1992; Harrad *et al.*, 1994) and in Slovenia through the dumping of industrial waste in the Krupa river during the manufacture of transformers. PCB contamination also occurred in the Balkan area, in the cities of Pancevo, Novi Sad, Belgrade, Kragujevac, in Serbia, after military intervention by NATO in spring 1999.

1.4.7 Food products

Since the early 1990s, food has been identified as the major route of human exposure to lipophilic and persistent organochlorines such as PCBs, PCDDs, and PCDFs. In populations that are not exposed to other known sources, dietary intake contributes to about 90% of the total daily intake of dioxin-like compounds including dioxin-like PCBs, and of this, food of animal origin contributes about 90% in various regions of the world (Schecter *et al.*, 1997; Büchert *et al.*, 2001; Llobet *et al.*, 2003a, b; Päpke & Fürst, 2003; Schecter *et al.*, 2003a, b; Charnley & Doull, 2005; Huwe & Larsen, 2005).

Similarly, it is generally accepted that the major route of exposure to non-dioxin-like PCBs, namely to PCB_6, is dietary intake, by consumption of fatty foodstuffs (IARC, 1978; IPCS, 1993; EFSA, 2005; Lindell, 2012). However, inhalation can also be a significant source of exposure (see Section 1.4.4).

Human food can become contaminated by PCBs via three main routes:

- uptake from the environment, by fish, birds, livestock (via food-chains), and crops;
- contamination of animal feed, by regular practices or accidentally;
- direct contamination of food, accidentally.

Data on PCB concentrations in food are reported in many different ways, making comparisons difficult. The number of congeners analysed differs between studies and often congeners are summed according to groups, such as indicator PCBs, DL-PCBs, or some other number of congeners. When using TEQs, the scheme used should be noted; also some studies report TEQ on the basis of bioassays such as the CALUX system as biological equivalents (BEQ). Results have been reported with different reference units (wet weight, dry weight, or lipid weight). Further difficulties in interpretation arise since different parts of fish or seafood are analysed (muscle, liver, skin, etc.) and PCB concentrations are also sometimes reported on the basis of prepared food (to account for changes by cooking or frying). Finally, the objectives of a study may bias the sampling strategy, often resulting in reporting of higher concentrations.

(a) PCB concentrations in food

Concentrations of DL-PCBs in various meats and dairy products from selected countries and regions are presented in Table 1.21.

(i) Polar regions and North America

PCB concentrations in food for polar regions and North America are summarized in Table 1.22. Domingo & Bocio (2007) reviewed the concentrations of PCB and PCDD/PCDF in marine species and human intake through fish and seafood consumption by different region-specific sections.

The traditional food items for indigenous peoples in the Arctic include lipid-rich tissue of high trophic-level animals. After long-range transport and biomagnification of PCBs in the Arctic marine food-chain, PCBs accumulate in edible animals like fish, seals and whales (AMAP, 2004). This dietary exposure led to PCB concentrations in Arctic inhabitants that exceeded those of individuals living at temperate latitudes (Dewailly *et al.*, 1993), but levels have been shown to decrease (AMAP, 2009). Likewise, PCBs in traditional food items have generally decreased (Rigét *et al.*, 2010).

(ii) Africa

Loutfy *et al.* (2006) investigated levels of WHO-TEQs from diet in Egypt, and determined a range of 6.59–9.98 pg TEQ/kg per day, with about 40% of this value due to DL-PCBs. This value exceeds the maximum WHO tolerable daily intake (TDI) of 4 pg TEQ/kg per day. The primary source was found to be dairy products, in which PCB concentrations were several times higher than in such products in more developed countries. Loutfy *et al.* (2007) determined the concentrations of PCDD/PCDF and dioxin-like PCBs in samples of fish and seafood (mullet fish, bolti fish, bivalves and crab) randomly acquired in local markets in Egypt. The upper-bound concentrations of dioxin-like PCBs ranged from 0.14 (bivalves) to 0.76 (mullet) pg WHO-TEQ/g wet weight, respectively.

Adu-Kumi *et al.* (2010) reported an average TEQ for dioxin-like PCBs in fish from two lakes in Ghana to be 0.7 pg WHO-TEQ/g.

(iii) Australia and New Zealand

In 2000–2001, 168 samples of 22 foods collected for the Australian Total Diet Survey were analysed for DL-PCBs and compared with those from other areas of the world (Table 1.21; Food Standards Australia New Zealand, 2004).

A more recent study reported PCB concentrations from composite samples of Australian farmed yellowtail kingfish (mean, 21 µg/kg; range, 8.6–29 µg/kg), mulloway (mean, 5.4 µg/kg; range,

Table 1.21 Concentrations of dioxin-like PCBs in selected foods from various countries and regions

Food	PCB concentration (range of means), pg TEQ/g lipid					
	Australia	Europe[a]	New Zealand[a,b]	North America[a]	Netherlands[c]	United Kingdom
Beef	0.03–0.11	–	0.0036–0.092	0.5	1.24	0.25–0.31[f]
Pork	0.04–0.07[d]	0.8	0.15–0.43[e]	0.02–1.7	0.23	–
Lamb	0.02–0.06	–	0.01–0.045	–	–	–
Poultry	0.18–0.24	0.7	0.018–0.14	0.3	1.72	0.47–0.53
Fish	9.46–9.5	0.03–9[h]	0.77	0.11–0.28[h]	0.412[g,h]	3.57–3.57
Eggs	0.04–0.11	0.2–0.6	0.05–0.11	0.029[h]	0.87	0.11–0.20
Milk	0.04–0.11	0.2–1.8	0.027–0.15	0.5	0.69	0.34–0.43
Bread	0.0003–0.005	–	0.00099–0.004	–	–	0.06–0.15
Butter	0.021–0.086	–	0.15–0.15	–	0.96	–

[a] Results reported in international toxic equivalents (I-TEQ), which are 10–20% lower than WHO-TEQs
[b] Results reported in the range of lower to middle bound
[c] Results reported as lower bound only
[d] Assumes bacon is representative of all pork products
[e] Pork meat
[f] Carcass meat
[g] Lean fish
[h] Reported on a fresh-weight basis
From Food Standards Australia New Zealand (2004)
PCB, polychlorinated biphenyl; TEQ, toxic equivalent

4.7–6 µg/kg) and manufactured feed (Padula *et al.*, 2012). The mean concentration of DL-PCBs was 2.1 pg TEQ/g (range, 1.2–2.8 pg TEQ/g) in kingfish, and 0.51 pg TEQ/g (range, 0.41–0.61 pg TEQ/g) in mulloway.

(iv) Asia

Concentrations of specific PCB congeners in samples of food from Asia are summarized in Table 1.23. In Japan, a study sponsored by the Ministry of Health and Welfare showed a more than 50% decrease in concentrations of three non-*ortho* substituted PCBs in human milk samples between 1973 and 1996 (Environment Agency of Japan, 1999). A report from the Republic of Korea demonstrated regular dietary exposure (Son *et al.*, 2012; Table 1.23). In China, Liu *et al.* (2011) determined concentrations of seven indicator PCBs in marine fish. The sum of PCB_7 ranged from 0.3 to 3.1 µg/g wet weight, with median and mean values of 6.4 ng/g wet weight and 398 ng/g wet weight, respectively (Table 1.23). The average concentrations and contributions of the seven specific congeners at four different sites are presented in Table 1.24. [It was noted that the concentrations found in this study were higher than in other parts of the world.]

(v) Europe

The major contributors to total exposure in Europe appeared to be milk and dairy products for almost all groups of infants and toddlers (Barr *et al.*, 2006; Becker *et al.*, 2009), and fish and seafood products for most of the adolescents, adults, elderly and very elderly groups (Langer *et al.*, 2007; Fréry *et al.*, 2009; ANSES, 2011).

The most comprehensive assessment of PCB concentrations in food was undertaken by the European Food Safety Agency (EFSA) (EFSA, 2005, 2010, 2012). For the 27 European Union Member States, and Switzerland and Norway, in a report that took all food groups together, the

Table 1.22 PCB concentrations in marine foods and estimated dietary intake in polar regions and North America

Country	Food analysed	PCB concentration	Estimated dietary intake	Comments	References
Polar regions					
Inuit of Quebec, Canada	ΣPCB10 in: Polar bear fat Seal blubber Arctic char muscle	 7 µg/g lipid 1 µg/g lipid 150 ng/g lipid		Female consumers of these foods had higher PCB concentrations in milk than a group in Southern Quebec	Dewailly *et al.* (1993)
West Greenland	ΣPCB10 in: Minke whale, beluga and narwhal blubber Halibut liver, kittiwake liver and muscle, minke whale skin, and seal blubber	 > 500 ng/g 50–500 ng/g	23 µg/day per person (3 µg/day per person if blubber food items are excluded from the diet)	Compared with the marine animals, concentrations in food sources from the terrestrial environment were characterized as low	Johansen *et al.* (2004)
North-western Territory, Canada	Food including cooked sucker flesh, raw beluga mattak (skin/blubber) and boiled Canada goose meat	Foodstuffs in the 50–500 ng/g group (Berti *et al.*, 1998)	Mean, 23 ng/kg bw per day Median, 11 ng/kg bw per day	Provisional tolerable daily intake was 300 ng/kg bw per day, based on Health Canada	Johansen *et al.* (2004)
Canada	Fish products from retail market	Geometric mean WHO-TEQ (pg/g wet weight): 0.06 (shrimp), 0.08 (tilapia), 0.92 (salmon)		No information on human exposure	Rawn *et al.* (2006)
North America					
USA (California coast)	Samples of a variety of fish	Mean I-TEQ: 109 pg/g lipid (non-*ortho* PCBs 77, 126, 169)		No information on human exposure	Brown *et al.* (2006)
USA, Maryland, Washington, DC, and North Carolina	Commercially wild caught and farm-raised fish	Bluefish, 800 ng/g ww (highest) Coho salmon, 0.35 ng/g ww (lowest)			Hayward *et al.* (2007)
USA	Salmon and canned sardines	Salmon: PCB-153, 1.2 ng/g ww; PCB-138, 0.93 ng/g ww Canned sardines: PCB-153 and PCB-138, 1.8 ng/g ww		Six of seven NDL-PCBs congeners were detected, with PCB-153 and PCB-138 at highest levels	Schecter *et al.* (2010)

NDL-PCB, non-dioxin-like polychlorinated biphenyls; ww, wet weight

Table 1.23 PCB concentrations in food in Asia

Country, region	Date	Source	PCBs measured	Concentration	Reference
Russian Federation					
Lake Baikal, Siberia	June 1991	Pelagic sculpin, omul, Baikal seal	61 PCB congeners using standards of Aroclor 1242, 1254, and 1260	Ranges, 2.7–2.8 mg/kg of lipid for pelagic sculpin, and 0.73–1.6 mg/kg of lipid for omul	Kucklick *et al.* (1994)
Lake Baikal, Siberia	May–June 1992	Five species of 35 fresh fish samples collected from Lake Baikal in 1993	Total PCBs using an equivalent mixture of Kanechlors 300, 400, 500, and 600 as standards	Mean, 1.7 ± 0.96 µg/g lipid	Nakata *et al.* (1995)
Lake Baikal, Siberia	1993	Three species of fish collected from Lake Baikal in 1993	Total PCBs using an equivalent mixture of Kanechlors 300, 400, 500, and 600 as standards	350 ± 350 ng/g ww	Nakata *et al.* (1997)
China					
Shanghai and its vicinity	2000–1	Various fish and seafood	Kanechlor-300, 400, 500, 600 as standards	Range, 0.20 (shrimp and mussel) to 2.5 (mackerel) ng/g ww	Nakata *et al.* (2002b)
North-eastern, Bohai Sea coastline	Early 2000s	Bivalves and gastropods	PCB mixture (EPA 68A-LCS)	Range, 62.3–344.9 ng/g lipid, for bivalves Range, 81.6–583.6 ng/g lipid, for gastropods	Zhao *et al.* (2005)
Dalian, Tianjin, and Shanghai		Fish and shellfish collected from local supermarkets	PCB-138 and PCB-153 were dominant, followed by PCB-101 and PCB-180	3.60 (0.83–8.04) ng/g ww Estimated daily intake: 1.83 ng/kg bw	Yang *et al.* (2006)
Guangzhou and Zhoushan	2003–4	Seafood (mainly harvested locally) purchased from local markets in Guangzhou and Zhoushan	PCBs 81, 77, 123, 118, 114, 105, 126, 167, 156, 157, 169, 189	Range, 1510–10 200 pg/g lipid	Jiang *et al.* (2007)
South China Sea, Bohai Sea, East China Sea, and Yellow Sea	2006–9	Marine fish	7 PCB congeners (28, 52, 101, 118, 138, 153, and 180); details in Table 1.24	Mean, 398 ng/g ww Median, 6.4 ng/g ww Range, 0.3–3100 ng/g ww	Liu *et al.* (2011)
South, Daya Bay and Hailing Bay	July 2007, December 2007	Fish	PCBs 31/28, 52, 44, 99, 149/118, 153, 138, 180, 170, 194, 101, 110, 147, 146, 187	Range, 1.5–4.0 ng/g ww	Yu *et al.* (2011a, b)
Nanjing	July, 2006	Fish and meat from 10 markets	PCBs 8, 18, 28, 52, 44, 66, 101, 81, 77, 123, 118, 114, 105, 153, 126, 138, 128, 187, 167, 156, 157, 170, 180, 189, 169, 195, 206, 209	Range, 0.87–15 ng/g ww for different fishery product; 5.1–20 ng/g ww for meat product	Su *et al.* (2012)
Fengjiang town (Taizhou)	2005–9	Rice hulls from a waste electrical and electronic-equipment dismantling area	PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 28, 52, 101, 138, 153, 180, 3, 15, 19, 202, 205, 208, 209 (dry weight basis)	44.1 ng/g (range, 12.8–124 ng/g) in 2005, 16.3 ng/g (range, 5.44–24.9 ng/g) in 2006, 9.01 ng/g (range, 2.57–22.8 ng/g) in 2007, 7.90 ng/g (range, 3.08–16.5 ng/g) in 2008, 7.39 ng/g (range, 3.80–10.7 ng/g) in 2009	Fu *et al.* (2012)

Table 1.23 (continued)

Country, region	Date	Source	PCBs measured	Concentration	Reference
Japan					
Ariake Sea		Shrimp, mussel, and mackerel		Range, 0.20–2.5 ng/g ww	Nakata *et al.* (2002a)
Japan		Fish and shellfish	PCB-126 and PCB-118 were the highest contributing congeners	In 1999: 0.98×10^{-3} WHO-$TEQ_{PCDD/PCDF/PCB}$ In 2004: 0.91×10^{-3} WHO-$TEQ_{PCDD/PCDF/PCB}$	Sasamoto *et al.* (2006)
Hirakata city, Osaka Prefecture	Unspecified	Domestic and imported seafood purchased from three food markets	PCBs 81, 77, 123, 118, 114. 105, 126, 167, 156, 157, 169, 180, 170, 189	Range, 13–40 182 pg/g ww	Ohta *et al.* (2008b)
Lao People's Democratic Republic					
Vientiane (Agent Orange-non-sprayed capital)	2001	Meat, fish, and dairy products from food markets	PCBs 37, 77, 126, 169, 81, 28, 33, 55, 60, 66, 74, 105, 114, 118, 122, 123, 124, 156, 157, 167, 189, 52, 101, 128, 138, 153, 170, 180, 187, 194, 206, 209	Range, 0.004–0.186 pg TEQ/g in fish samples; 0.011– 0.063 pg TEQ/g in meat and dairy products	Schecter *et al.* (2003a)
Republic of Korea					
		Muscle of sport and market fish	22 PCB congeners	23.0 (4.48–95.6) ng/g ww (sport fish) 8.91 (2.96–68.2) ng/g ww (market fish)	Yim *et al.* (2005)
		40 species of marine organism	DL-PCBs	0.4×10^{-3} ($0.008–0.6) \times 10^{-3}$ WHO-TEQ ww	Moon & Ok (2006)
	2005 to 2007	26 marine species (n = 78) collected annually during 2005–2007 from a large fish market in Busan	PCBs 8, 18, 28, 29, 44, 52, 87, 101, 105, 110, 118, 128, 138, 153, 170, 180, 187, 194, 195, 200, 205, 206	Range, 0.2–41 ng/g ww	Moon *et al.* (2009)
Singapore					
Singapore (cont.)	June 2002 to June 2003	Twenty types of seafood from local supermarkets	PCBs 17, 18, 28/31, 33, 44, 49, 52, 70, 74, 82, 87, 90, 101, 95, 99, 105, 110, 118, 128, 132, 138, 149, 151, 153, 156, 169, 170, 171, 177, 180, 183, 187, 194, 199, 201, 205, 206, 208, 209	Mean, 3.72 ng/g ww (range, 0.61–28.47 ng/g ww)	Bayen *et al.* (2005)

DL-PCBs, dioxin-like polychlorinated biphenyl; ww, wet weight

Table 1.24 PCB concentrations in marine fish from China

PCB	PCB concentration (n/g ww)							
	South China Sea		Boahi Sea		East China Sea		Yellow Sea	
	Average concentration (n/g ww)	Contribution (%)	Average concentration (n/g ww)	Contribution (%)	Average concentration (n/g ww)	Contribution (%)	Average concentration (n/g ww)	Contribution (%)
PCB-25	0.10	5.0	6.7	10.7	38.8	7.5	111.9	11.1
PCB-52	0.13	6.4	4.6	7.3	40.8	7.8	64.2	6.4
PCB-101	0.35	17.3	8.6	13.7	48.3	9.3	88.1	8.7
PCB-118	0.22	10.7	12.1	19.3	43.9	8.4	106.2	10.5
PCB-138	0.66	32.4	11.2	17.8	167.1	32.1	336.5	33.4
PCB-153	0.39	18.8	16.3	26.0	136	26.2	248.8	24.7
PCB-180	0.19	9.4	3.3	5.3	45.0	8.7	52.4	5.2
Σ 7 PCBs	2.0	–	62.8	–	520	–	1008	–

PCB, polychlorinated biphenyl; ww, wet weight
Data from Liu *et al.* (2011)

upper bound (lower bound) for the 50th, 90th and 95th percentiles were < 0.005 (< 0.005), 0.02 (0.01) and 0.03 (0.01) pg WHO_{2005}-TEQ/g wet weight for PCDD/PCDF, respectively. For the total TEQ, the upper bound (lower bound) concentrations were 0.01 (< 0.005), 0.04 (0.02) and 0.07 (0.04) pg WHO_{2005}-TEQ/g wet weight, respectively (EFSA CONTAM, 2012). Infant formulae showed upper bound concentrations below the current maximum levels (0.2 pg WHO_{2005}-TEQ/g wet weight), with highest concentrations found in ready-to-eat meals containing fish or meat. Overall, a decrease in concentrations of DL-PCBs was observed for the three food groups available: "raw milk and dairy products," "hen eggs and egg products" and "muscle meat from fishes other than eels." Feed and food of animal origin contained higher concentrations of PCDD/PCDF and DL-PCBs combined (the non-*ortho* PCBs were the main contributors to the total TEQs) than foods from plant origin. PCB-153, PCB-138, and PCB-180 represented altogether 36.9–97.8% of the sum of PCB_6. The maximum levels were exceeded in 9.7% of the food samples and 2.3% of the feed samples for PCDD/PCDF and DL-PCBs combined, and in 3.0% of the food samples and 2.4% of the feed samples for the PCB_6. With respect to food categories, lower PCB concentrations were found in meat from sheep, eggs from battery rearing, farmed salmon and trout, and farm milk (which however showed higher concentrations of PCDD/PCDF and DL-PCBs combined than milk from bulk) (EFSA, 2012).

The Baltic Sea area is heavily contaminated with persistent organochlorine compounds, including PCBs (Kiviranta *et al.*, 2003), as is clearly attested by samples of fatty fish from the eastern coast in Sweden (Svensson *et al.*, 1995). In the most contaminated feed group, the highest relative contribution to the WHO_{2005}-TEQ_{total} came from non-*ortho* PCBs, up to twice the average contribution (EFSA, 2012).

(b) Estimated daily dietary intake

In Europe, more than 90% of PCB exposure in the general population is via food consumption (EFSA, 2005; Table 1.25). Average daily dietary intakes of the sum of PCB_6 are in the range of 10–45 ng/kg bw for adults, and two and a half times higher in children. Limited exposure data for young children indicate that the average daily intake (breastfeeding excluded) of the sum of PCB_6 is about 27–50 ng/kg bw. Overall, the non-*ortho* PCBs represented 21.0–74.9% of the WHO_{2005}-TEQ_{total} of PCDD/PCDF and DL-PCBs combined in food (EFSA, 2012), and the mono-*ortho* PCBs represented no more than 12% of the WHO_{2005}-TEQ_{total}. In the most contaminated samples, such as products from aquatic animals and from ruminants, the relative contribution of the non-*ortho* PCBs ranged from 34.2% to 86.1%. Most likely due to an effect of the European risk management measures, a decrease in exposure to the sum of PCB_6 was observed between 2002–2004 and 2008–2010 in most but not all population groups, and it was estimated between 2.0% and 75.6%.

In the USA, the daily dietary intake of PCBs for adults decreased from 1978 (0.027 µg/kg bw) until 1986–1991 (< 1 ng/kg bw) (IPCS, 2003). Mean daily intakes for infants during the same period decreased from 11 to < 1 ng/kg bw. However, trends during 1991–1997 did not appear to decrease, and ranges of daily dietary intake were 3–5 ng/kg bw for adults, and 2–12 ng/kg bw for children of different ages (IPCS, 2003).

Daily dietary intake of PCBs from countries in Asia are presented in Table 1.26. In China, the estimated daily intake from four food groups of animal origin ranged from 0.09 to 0.59 pg TEQ/kg bw for DL-PCBs, which is lower than the daily intake in some developed countries (Liu *et al.*, 2013). A survey of food items on the market and typical consumption patterns in Japan reported a daily intake for the general population of 2.60 pg TEQ/kg bw per day (Koizumi *et al.*, 2005). Of

Table 1.25 Dietary exposure to PCBs for an average consumer on the European market

Food group	Mean ΣPCBs (ng/g)	Consumption (g/day)			Exposure (ng/day)		
		Italy	France	Sweden	Italy	France	Sweden
Cereals and cereal products	0.0213	270	218	292	6	5	6
Fruits and vegetables	0.0495	498	313	387	25	15	19
Eggs	0.73	18	17	15	13	12	11
Fats and oils	5.05	38	18	24	192	91	121
Meat and meat products	1.52	134	117	143	204	178	218
Offals	0.74	3	3	7	2	2	5
Fish and fish products	12.50	43	32	35	538	400	438
Milk	0.17	124	106	343	21	18	59
Cheese and dairy products	0.98	87	100	45	86	98	44
Total (ng/kg bw per day)		–	–	–	18.1	13.7	15.4
Total (ng/kg bw per day) for a high consumer of meat and meat products		–	–	–	22.0	17.6	18.9
Total (ng/kg bw per day) for a high consumer of fish and fish products		–	–	–	40.4	31.8	33.3

PCB, polychlorinated biphenyl
Adapted from EFSA (2005)

Table 1.26 Estimated daily dietary intake of PCBs in Asia

Country, region	Date	Source	PCBs measured	Mean daily intake	Reference
Japan, Fukuoka Prefecture	1969–70	Patients Individual consumption of oil was estimated by taking into account age, sex and the number of meals at home	PCBs, PCDFs, and PCQs	Estimated total intake: PCBs, 633 mg PCDFs, 3.4 mg PCQs, 596 mg	Hayabuchi *et al.* (1979)
Japan, eight sites from Hokkaido to Okinawa	1995 survey	Food duplicate study 40 women (mean age, 52 years)	11 PCB congeners (74, 99, 118, 138, 146, 153, 156, 163, 170, 180, and 182)	165.9 ng/day	Koizumi *et al.* (2005)
Japan, 75 different areas of 25 prefectures	Not reported	Food duplicate study 374 subjects, 86 men and 288 women (mean age, 48.0 years; range, 17–72 years)	12 PCBs	Mean PCB intake, 0.59 pg/kg bw per day Median PCB intake, 0.39 pg/kg bw per day	Arisawa *et al.* (2008)
Republic of Korea	2010	Estimated dietary intake 200 individual food samples from 40 different foodstuffs	62 PCB congeners, including 7 indicator PCBs and 12 DL-PCBs (PCB-1, 3, 4, 8, 10, 15, 18, 19, 22, 33, 37, 44, 49, 54, 70, 74, 87, 95, 99, 104, 110, 112, 128, 149, 151, 155, 158, 168, 170, 171, 177, 178, 183, 187, 188, 191, 194, 199, 201, 202, 205, 206, 208, and 209)	9.9 ng/kg bw per day	Son *et al.* (2012)

DL-PCBs, dioxin-like polychlorinated biphenyls; PCDFs, polychlorinated dibenzofurans; PCQs, polychlorinated quaterphenyls; ww, wet weight

these, 2.41 pg TEQ/kg bw per day was from ingestion of food, while inhalation and soil ingestion contributed only to 0.19 pg TEQ/kg bw per day. A "typical" Japanese person receives 120.7 pg TEQ per day through food consumption (mainly fish/shellfish, followed by meat/eggs).

In specific subpopulations with high dietary PCB exposure, such as Baltic Sea fishermen, the daily intake from fish of the sum of PCB_6 was estimated at 40 ng/kg bw, corresponding to a total daily intake of the sum of non-dioxin-like PCBs of 80 ng/kg bw, before taking into account the rest of the diet (Lindell, 2012).

In breastfed infants, the most recent WHO study of PCB exposure reported a mean daily intake of about 1600 ng/kg bw (range, 230–7300 ng/kg bw per day) for total PCB_6. Thus, exposure of infants to PCB_6 (and DL-PCBs) through human milk is about two orders of magnitude higher than the average daily intake by adults.

1.4.8 Occurrence in manufactured products other than commercial PCB preparations

In addition to commercial PCB preparations, many manufactured products contain PCBs as a result of contact with PCB products, as contaminants during manufacture, or as degradation products of other chlorinated compounds. For example, PCBs have been found in various paint pigments (Hu & Hornbuckle, 2010; Kuusisto *et al.*, 2006). Electronic equipment contains PCBs, which are released during dismantling.

Since the sampling and determination of the presence of PCBs is a difficult process, the Basel Convention has established a so-called "grey list" of materials and equipment that are suspected to contain PCBs (Basel Convention, 2003):

- Cable insulation
- Rubber and felt gaskets
- Thermal insulation material including fibreglass, felt, foam and cork
- Transformers, capacitors (also contained in electronic equipment)
- Voltage regulators, switches, bushings and electromagnets
- Adhesives and tapes
- Oil, including that contained in electrical equipment and motors, anchor windlasses, hydraulic systems
- Surface contamination of machinery and other solid surfaces
- Oil-based paint
- Caulking
- Rubber isolation mounts
- Foundations mounts
- Pipe hangers
- Light ballasts
- Plasticizers.

1.4.9 Population biomonitoring

(a) Blood

The presence of PCBs in serum or blood may reflect exposure from any source (Dewailly *et al.*, 1988). Results from different studies in humans have indicated that measurements of PCBs in serum generally reflect cumulative past exposure. Many PCB congeners can remain in the body for years after exposure, although some of the less chlorinated congeners are more volatile and consequently show shorter residence times.

(i) North America

Hopf *et al.* (2009a) provided an extensive review of reports on background levels of PCBs in the USA population. They concluded that serum concentrations increased up to 1979 and decreased after that, but that the background levels are still of concern. The NHANES survey over the period 2002–2004 reported increasing

concentrations of PCBs with age, and concentrations were higher in men than in women, and higher in African-Americans and Caucasians than in Mexican-Americans (Patterson *et al.* 2009). Sjödin *et al.* (2004) showed a decline in concentrations of PCB-153 between 1985 and 2002 in pooled samples from the NHANES study.

Several studies have looked at specific populations living near specific contaminated sites or eating contaminated fish (Table 1.27).

Serum concentrations for the sum of 17 congeners in Viet Nam veterans were 167.5 ng/L lipid adjusted, of which the major portion (116.6 ng/L) were di-*ortho* congeners (Schecter *et al.*, 1996).

Jarrell *et al.* (2005) determined the sum of 24 congeners in pregnant women in Canada, and reported a mean value of 0.78 ng/L wet weight.

Because the less chlorinated PCBs are more volatile, teachers working in a school where caulk containing PCBs was used showed serum congener profiles that were enriched in less chlorinated congeners (Herrick *et al.*, 2011).

DeCaprio *et al.* (2005) reported finding a pattern of PCB congeners in serum specific of young native Americans living near a PCB-contaminated waste site. This pattern was not clearly observed in older individuals because it was obscured by the greater concentrations of more persistent congeners, coming primarily from dietary exposure.

(ii) Europe

Several European studies on human biomonitoring have reported blood PCB concentrations in adults or children (summarized in Table 1.28). Past environmental contamination in industrial areas has polluted surrounding soils and forage, leading in turn to high blood PCB concentrations in the adult population. Age-related accumulation of PCBs has been observed in many studies (Patterson *et al.*, 1994; Apostoli *et al.*, 2005; Park *et al.*, 2007), and may be partially explained by historical high levels of exposure in the 1970s.

In Germany, Environmental Surveys (GerES) were carried out in 1998 (Becker *et al.*, 2002) and during 2003–2006 (Becker *et al.*, 2009). GerES data show mean blood concentrations for the sum of PCBs of 1.3–1.7 µg/L in 1998 and of 286 ng/L in the more recent survey, with strong difference (factor of 5.6) between age groups 18–25 and 66–69 years. In Belgium in 2007–2011 (Schoeters *et al.*, 2011), the Flemish Human Environmental Survey reported average blood PCB concentrations of 333 ng/g lipid. Average concentrations in the United Kingdom in 2003 were 170 ng/g lipid (Thomas *et al.*, 2006). In Spain in 2004–2008, concentrations of the most common PCBs were in the range of 21.8 to 38.9 ng/g lipid (Ibarluzea *et al.*, 2011). In France, blood analysis in the general adult population was first carried out in 1986 (Dewailly *et al.*, 1988) and then in 2006–2007 (French Nutrition and Health survey; Fréry *et al.*, 2013). The reported blood PCB concentrations in populations in industrial polluted areas such as Italy (Turci *et al.*, 2004; Apostoli *et al.*, 2005; Turrio-Baldassarri *et al.*, 2008) and Slovakia (Jursa *et al.*, 2006) were high compared with those in non-occupationally exposed populations such as in Sweden (Salihovic *et al.*, 2012). In the Faroe Islands (Denmark), high concentrations of PCBs and hydroxylated PCBs in serum samples from pregnant women were attributed to the traditional diet, made of pilot whale meat, blubber and other marine food (Fängström *et al.*, 2002).

The most frequently detected di-*ortho*-chlorine-substituted PCBs in population studies are PCB-138, PCB-153, and PCB-180 (Glynn *et al.*, 2000), accounting for 65–78% of the measured sum of total PCBs (Needham *et al.*, 2005). The seven PCB indicator congeners (118, 138, 153, 156, 170, 180, and 194) contributed to 99% of the total PCB levels, with a modest contribution from dioxin-like congeners (Apostoli *et al.*, 2005).

In several countries in the European Union, a clear decrease in blood concentrations of PCBs has been observed in the last two decades. Overall,

Table 1.27 Serum concentrations of PCBs after consumption of PCB-contaminated fish, North America

Country, region	Sample	PCBs measured	Mean ng/g (ppb)	Reference
North Canada, Nunavik	Inuit women, *n* = 159	Sum of 14 congeners	313.2 ± 2 Range, 71.3–1951.3	Muckle *et al.* (2001)
USA, St Lawrence River	Native American adults, *n* = 753	Sum of 101 congeners	4.39 ± 4.18	DeCaprio *et al.* (2005)
USA, St Lawrence River	Native American adolescents		0.71 ± 0.668 (if not breastfed) 0.95 ± 0.806 (if breastfed)	Schell *et al.* (2008)
USA, Great Lakes	Fish consumers, *n* = 293 Fishing-ship captains, men	Sum of 89 congeners in µg/L (ppb) wet weight	4.2 (2.7), in 1994–95 2.8 (2.0), in 2001–05 6.3 (5.0), in 1994–95 1.2 (0.9) – 3.8 (3.0), in 2001–05	Knobeloch *et al.* (2009)
USA, Anniston, Alabama	Adult residents, *n* = 394	Sum of 35 congeners	4.72 ± 11.05 Range, 0.09–170.42	Goncharov *et al.* (2011)

PCB, polychlorinated biphenyl

mean whole blood concentrations of PCB-138, PCB-153, and PCB-180 appear to have decreased by approximately 80% in 20 years (Link *et al.*, 2005; Hagmar *et al.*, 2006; Agudo *et al.*, 2009; AMAP, 2009). Nevertheless, compared with North America (CDC, 2005), serum concentrations of PCB-138, PCB-153, and PCB-180 were higher by two- to fivefold in Germany in 1998 (Heudorf *et al.*, 2002), or Italy in 2001–2003 (Turci *et al.*, 2004; Apostoli *et al.*, 2005; Needham *et al.*, 2005). Similarly, serum concentrations of hydroxylated PCBs and methylsulfonyl-substituted metabolites of PCBs were higher by two to threefold in a contaminated area in a study in Slovakia (Hovander *et al.*, 2006).

(iii) Asia

In Asia, PCB concentrations in several biological samples (including serum or whole blood, umbilical cord blood, hair, breast milk, adipose tissue, liver, kidney, and lung tissues) showed a wide range (Table 1.29; Schecter *et al.*, 2003a). Data specific to the Yusho and Yucheng patients are presented in Table 1.30 and Table 1.31, respectively.

(iv) South and Central America

Rodríguez-Dozal *et al.* (2012) analysed serum samples from pregnant women in Mexico for 19 congeners and Aroclor 1260. For Aroclor 1260 [calculated as the sum of PCB-138 and PCB-153 multiplied by 5.2], they reported regional differences (mean concentration, 31.1 ng/g lipid) and elevated concentrations from residents of Merida (maximum, 546.2 ng/g lipid). Trejo-Acevedo *et al.* (2012) measured serum PCB concentrations (sum of 14 congeners) from children living in a malaria-endemic area of Mexico, and reported a mean serum PCB concentration of 5892 ± 3895.7 ng/g lipid. In an analysis of PCB congeners in maternal blood of women in Sao Paulo State, Brazil, PCB-118, PCB-138, and PCB-153 were detectable in more than 70% of samples, and their concentrations were almost double in women from industrial areas compared with women from rural areas (Rudge *et al.*, 2012).

(v) Africa

Röllin *et al.* (2009) reported overall low blood concentrations of PCBs (99, 118, 138, 153, 170, 180 and 187) in delivering mothers from seven geographical regions in South Africa. Large regional differences were observed, with women

Table 1.28 Blood concentrations of PCBs in various European countries

Country	Reference/study	Period	Age (years)	Number	PCBs measured	Mean	95th percentile
France	Dewailly *et al.* (1988)	1986	Men: 38	569	Σ 7 PCBi	4020 ng/L	5000 ng/L
	Fréry *et al.* (2009)	2005	30–65	1030	138, 153, 180	347 ng/g lipid	714 ng/g lipid
	ANSES (2011)	2009–10	18–75	606 16	138, 153, 180	305 ng/g lipid 681 ng/g lipid	1368 ng/g lipid 3150 ng/g lipid
	Fréry *et al.* (2013)	2006–7	18–74	386	Σ 6 PCBi	287 ng/g lipid 1858 ng/L	721 ng/g lipid 4977 ng/L
Germany	GerES III GerES IV (2008)	1998 2003–6	18–69 7–14	2815 1079	138, 153, 180	1570 ng/L 286 ng/L	5000 ng/L 980 ng/L
United Kingdom	Thomas *et al.* (2006)	2003	22–80	151	Σ 31 congeners	170 ng/g lipid	670 ng/g lipid
Belgium	Schoeters *et al.* (2011)	2007–11	50–65	1530	138, 153, 180	333 ng/g lipid	
Italy	Turci *et al.* (2004)	2001–3		162	Total PCBs	2480 ng/L	5240 ng/L
	Apostoli *et al.* (2005)	2003	20–79	311	Σ 24 congeners	897 ng/g lipid	2643 ng/g lipid
	Turrio-Baldassarri *et al.* (2008)	2004	Men: 51	94	Σ 6 congeners	866 ng/g lipid	
Slovakia	Jursa *et al.* (2006)	2001–2	20–70	315	Σ 45 congeners	CA:5863 ng/g lipid RA:1245 ng/g lipid	Max: 55 334 ng/g lipid Max: 9015 ng/g lipid
	Park *et al.* (2007)	2002–4	Pregnant	CA: 762 RA: 341	118, 153, 105, 138, 180, 170	CA: 734 ng/g lipid RA: 351 ng/g lipid	CA:2105 ng/g lipid RA: 469 ng/g lipid
Spain	Agudo *et al.* (2009)	1992–6	35–64	953	138, 153, 180	459 ng/g lipid	
	Ibarluzea *et al.* (2011)	2004–8	Pregnant	1259	138, 153, 180	88 ng/g lipid	
Sweden	Salihovic *et al.* (2012)	2001–4	70	Men: 495 Women: 517	138, 153, 180	Men: 600 ng/g lipid Women: 517 ng/g lipid	753 ng/g lipid 664 ng/g lipid

CA, contaminated area; PCB, polychlorinated biphenyl; RA, reference area; PCBi, indicator PCBs

Table 1.29 PCB concentrations in biological samples from populations in Asia

Country, region, Year	Subjects, participants	Samples	PCBs measured	Mean concentrations (standard deviation or range)	Reference
Taiwan, China 1994	Pooled blood of 50 women	Blood serum	PCBs 28, 52, 74, 66, 101, 153, 138, 187, 183, 156, 157, 180, 170	386 ng/g lipid	Guo *et al.* (1997)
Central Taiwan, China 2001	30 primiparous women (mean age, 27.8 yr; range, 20–35 yr)	Breast milk	PCBs 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189	4.87 (SD 8.04) pg TEQ/g lipid	Chao *et al.* (2003)
Central Taiwan, China 2000–1	20 pregnant women; mean age, 28 yr (range, 25–35 yr)	Placenta, milk, venous blood, and cord blood	12 DL-PCBs and 6 indicator PCBs	DL-PCBs: 5292 pg/g lipid in placenta, 10 170 pg/g lipid in milk, 9496 pg/g lipid in venous blood, and 3577 pg/g lipid in cord blood Indicator PCBs: 32 457 pg/g lipid in placenta, 55 425 pg/g lipid in milk, 36 416 pg/g lipid in venous blood, and 37 758 pg/g lipid in cord blood	Wang *et al.* (2004)
Taiwan, China 2004	Pooled blood plasma of 10 blood donors	Blood plasma	33 PCB congeners included PCB-8, 37, 44, 49, 52, 60, 66, 70, 74, 77, 82, 87, 99, 101, 105, 110, 114, 118, 126, 128, 138, 153, 156, 157, 158, 166, 169, 170, 179, 180, 183, 187, and 189.	187 ng/g lipid	Hsu *et al.* (2005)
East China July 11–13, 2006	64 male workers, aged 18–60 yr	Hair	PCBs (1668A-LCS, 1668A-IS)	Mean 1 600 pg/g dw (55 400–7 200 000 pg/g dw)	Wen *et al.* (2008)
China, Zhejiang April 2007 to January 2008	Surgical patients newly diagnosed for cancer (mean age, 65 yr; range, 32 to 94 yr)	Kidney, liver and lung tissues	27 PCB congeners	Median (range) in ng/g lipid: 382.15 (86.92–1403.92) (kidney); 460.00 (89.19–1742.57) (liver); 304.64 (104.85–373.25) (lung)	Zhao *et al.* (2009)
China, Shenzhen July to November 2007	60 samples from primiparous women living in areas not polluted by POPs (mean age, 28 yr; range 20–34 yr)	Breast milk	PCBs 28, 52, 101, 138, 153, 180, 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189	DL-PCBs: median (range): 4580 (1964–13 967) pg/g fat Indicator PCBs: 13.2 (3.4–39.2) pg/g fat	Deng *et al.* (2012)
China, Zhejiang Province 2008	74 women in rural areas (mean age, 25.0 yr; range, 19–29 yr) and in urban areas (mean age, 26.5 yr; range, 22–29 yr)	Breast milk	PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189, 28, 52, 101, 138, 153, 180	42 774 ± 27 841 pg/g lipid (urban group) 26 546 ± 11 375 pg/g lipid (rural group)	Shen *et al.* (2012)
India, six different locations, 2009	55 mothers, reproductive age, ranged 21–38 yr	Breast milk	$^{13}C_{12}$-labelled PCBs	3.1 to 5 400 ng/g lipid weight	Devanathan *et al.* (2012)

Table 1.29 (continued)

Country, region, Year	Subjects, participants	Samples	PCBs measured	Mean concentrations (standard deviation or range)	Reference
India, Bangalore and Chidambaram 2007	25 e-waste recycling workers	Serum	62 PCB congeners	360 pg/g ww	Eguchi *et al.* (2012)
India, Bangalore and Chidambaram 2007	20 residents near a coastal area	Serum	62 PCB congeners	140 pg/g ww	Eguchi *et al.* (2012)
Islamic Republic of Iran, Ahvaz and Noushahr cities, and the countryside of Noushahr November 2007 to January 2008	16 pregnant women in Noushahr (mean age, 26 yr; range, 16–43 yr) 21 pregnant women in Ahvaz (mean age, 27 yr; range, 18–36 yr) 19 pregnant women in countryside of Noushahr (mean age, 25 yr; range, 15–36 yr)	Hair	PCBs 28, 52, 101, 118, 138, 143, 153, 180	Median (range): 9 (4–140) ng/g in Noushahr 8 (4–14) ng/g in Ahvaz 2 (undetected –15) ng/g in Noushahr countryside	Dahmardeh Behrooz *et al.* (2012)
Japan, Fukuoka Prefecture April to June, 1991	Nine normal women (mean age, 30 yr; range, 25–32 yr)	Breast milk	PCB-77, PCB-126, PCB-169	Mean coplanar PCBs, 21.3 pg TEQ/g fat Mean PCB-77: 12.4 pg/g fat; Mean PCB-126: 183.7 pg/g fat; Mean PCB-169: 65.7 pg/g fat TEFs as proposed by the NATO-CCMS (1988), and those of the coplanar PCBs were calculated using data reported by Safe (1990).	Matsueda *et al.* (1993)
Japan September 1994 to November 1996	31 normal volunteers (age, 20–61 yr)	Sebum, and blood	PCB-77, PCB-126, PCB-169	Mean PCBs, 447.3 pg/g lipid (sebum), and 204.6 pg/g lipid (blood)	Iida *et al.* (1999)
Japan 1998–9	28 patients with various illnesses (age, 19–87 yr)	Liver and adipose tissue	Non-*ortho*-PCBs	Mean (range): 20 (2.8–91) TEQ/g lipid (liver tissue) 17 (2.7–57) pg TEQ/g lipid (adipose tissue)	Takenaka *et al.* (2002)
Japan 1999–2000	80 women (mean age, 36.9 yr; range, 26–43 yr)	Serum	36 PCBs	Median, 0.46 (25th percentile, 0.35; 75th percentile, 0.66) nmol/g lipid	Tsukino *et al.* (2006)

Table 1.29 (continued)

Country, region, Year	Subjects, participants	Samples	PCBs measured	Mean concentrations (standard deviation or range)	Reference
Japan, Fukuoka Prefecture 2002–3	127 normal controls (age, 68.0 yr; SD, 5.4 yr)	Blood/serum	PCB-77, PCB-126, PCB-169	11.9 pg TEQ/g lipid	Todaka *et al.* (2007a)
Japan Born 1950–86	15 samples from 9 healthy subjects	Preserved umbilical cord	Dioxin-like PCBs (81, 77, 123, 118, 114, 105, 126, 167, 156, 157, 169, 189)	Mean (range): 2700 (250–12 000) pg/g	Aozasa *et al.* (2008)
Japan, Sapporo City July 2002 to July 2004	101 primiparous pregnant women (mean age, 28.8 yr; range, 18–40 yr) and 94 multiparous pregnant women (mean age, 32.3 yr; range, 28–47 yr)	Blood	PCBs 28, 44, 47/48, 49, 52/69, 56/60, 63, 66, 70, 71, 74, 85, 87, 92, 93/95/98, 99, 101, 107/108, 110, 117, 128, 130, 132, 134, 135, 137, 138, 139, 141, 146, 147, 151, 153, 163/164, 165, 170, 172, 177, 178, 179, 180, 181, 182/187, 183, 191, 194, 195, 196/203, 198/201, 200, 202, 205, 206, 207, 208, and 209	Mean (range): 114.5 ± 61.0 (42.2–329.3) ng/ g lipid (primiparous) 100.2 ± 48.2 ng/g lipid (31.5–258.0) (multiparous)	Todaka *et al.* (2008a)
Japan, Sapporo City, Hokkaido Prefecture July 2002 to July 2004	60 mothers (mean age, 31 yr; range, 21–47 yr)	Blood and breast milk	PCBs 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189	Mono-*ortho* PCBs, 13.4 ± 5.8 ng/g lipid (blood) and 14.4 ± 8.2 ng/g lipid (breast milk) Non-*ortho* PCBs 97 ± 10 pg/g lipid (blood); and 60 ± 28 pg/g lipid (breast milk)	Todaka *et al.* (2008b)
Japan, Fukuoka and Nagasaki prefectures Born 1970–3	Five babies born to healthy mothers	Preserved umbilical cord	DL-PCBs (77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189)	0.1 pg TEQ/g dw	Nagayama *et al.* (2010)
Japan, Sapporo City July 2002 to October 2005	119 primiparous mothers (mean age, 30 yr; range, 21–40 yr)	Blood and breast milk	Non-*ortho* PCBs, mono-*ortho* PCBs, and 56 NDL-PCBs	120.2 ± 67.3 ng/g lipid (blood) 90.4 ± 51.6 ng/g lipid (breast milk)	Todaka *et al.* (2010)
Japan, Sapporo City July 2002 to October 2005	514 pregnant women (mean age, 32 yr; range, 22–41 yr)	Blood and breast milk	Non-*ortho* PCBs, mono-*ortho* PCBs, and 56 NDL-PCBs	Non-*ortho* PCBs, 77 ± 32 pg/g lipid (blood) and 51 ± 21 pg/g lipid (breast milk) Mono-*ortho* PCBs, 11.7 ± 5.7 pg/g lipid (blood) and 10.0 ± 5.2 ng/g lipid (breast milk) NDL-PCBs, 107 (16–326) ng/g lipid (blood) and 73 (12–252) ng/g lipid (breast milk)	Todaka *et al.* (2011)

Table 1.29 (continued)

Country, region, Year	Subjects, participants	Samples	PCBs measured	Mean concentrations (standard deviation or range)	Reference
Republic of Korea, Kyungpook May 2007 to May 2008	53 female myoma patients (mean age, 47 yr; range, 40–68 yr)	Adipose tissue	PCBs 8, 18, 28, 29, 44, 52, 87, 101, 105, 110, 118, 128, 138, 153, 170, 180, 187, 194, 195, 200, 205, 206	270 ± 140 ng/g lipid	Moon *et al.* (2012)
Russian Federation, Irkutsk Region 1992	Three groups of Siberians	Blood	PCBs 77, 126, 169	Mean TEQ, 2.0–25.2 ppt	Schecter *et al.* (2002)
Viet Nam, areas sprayed with Agent Orange 2006	Potentially exposed persons	Blood	Coplanar PCBs, mono-*ortho* PCBs	Coplanar PCBs TEQ, 1.1–5.6 pg/g lipid Mono-*ortho* PCBs TEQ, 1.8–7.3 pg/g lipid	Schecter *et al.* (2006)

DL-PCB, dioxin-like polychlorinated biphenyl; dw, dry weight; NDL-PCB, non-dioxin-like polychlorinated biphenyl; TEQ, toxic equivalent; ww, wet weight; yr, year

Table 1.30 PCB, PCDF, and PCDD concentrations in biological samples from the Yusho population, Japan

Region Period	Subjects/ participants	Sample	PCB measured	Concentration (mean, median, range)	Reference
Fukuoka, Saga, and Ishigaki cities 1970 in Saga; 1972 in Fukuoka; and 1972 in Ishigaki	*n* = 11 in Saga; *n* = 19 in Fukuoka; and *n* = 12 in Ishigaki	Adipose tissue, and breast milk	Mean PCBs	In Saga, PCBs in adipose tissue, mean, 2.6 (range, 0.5–5.3) ppm fat basis In Fukuoka, PCBs in breast milk, mean, 1.2 (range, 0.3–5.6) ppm fat basis In Ishigaki, PCBs in breast milk, mean, 0.4 (0.1–0.7) ppm fat basis	Masuda et al. (1974)
Japan 1973		Blood (*n* = 41), adipose tissue (*n* = 6), liver (*n* = 5)	PCB-118, 105, 153, 132, 156, 170, 180	Mean, 6.7 ppb in blood Mean, 2.5 ppm in adipose tissue Mean, 0.1 ppm in the liver	Masuda & Yoshimura (1982)
Fukuoka Prefecture 1981	59 Yusho patients aged > 40 years not receiving antihypertensive treatment	Blood/serum	Total PCBs	5.1 ± 2.3 ppb for men 6.4 ± 5.3 ppb for women	Akagi & Okumura (1985)
Japan 1988	259 patients (136 men and 123 women)	Blood/serum	Specific congeners not mentioned	Geometric means of PCBs and triglyceride: 3.84 (95% CI, 3.54–4.17) ppb and 114.3 (95% CI, 106.6–122.6) mg/dL, respectively Arithmetic mean of PCBs: 4.8 ppb (range, 0.6–320 ppb)	Hirota et al. (1993)
Japan September 1994 to November 1996	39 Yusho patients	Sebum, blood serum	PCB-77, PCB-126, PCB-169	428.1 pg/g lipid in sebum, and 390.7 pg/g lipid in blood	Iida et al. (1999)
Japan 2002	279 Yusho patients	Blood/serum	PCB-77, PCB-81, PCB-126, PCB-169	3.383 ± 2.765 (range 0.25–25.1) ppb	Uenotsuchi et al. (2005)
Japan 2002–3	279 Yusho patients in 2002 and 269 Yusho patients in 2003.	Blood/serum	PCB-77, PCB-81, PCB-126, PCB-169	125.0 pg-TEQ/g lipid	Todaka et al. (2005)
Fukuoka Prefecture 2002	279 Yusho patients and 92 Yusho-suspected persons	Blood/serum	PCBs 81, 77, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189	Yusho patients: Non-*ortho* PCBs, 12.3 pg TEQ/g lipid; mono-*ortho* PCBs, 25.0 pg TEQ/g lipid Yusho-suspected persons: Non-*ortho* PCBs, 10.0 pg TEQ/g lipid; mono-*ortho* PCBs, 8.8 pg TEQ/g lipid	Todaka et al. (2007a)

Table 1.30 (continued)

Region Period	Subjects/ participants	Sample	PCB measured	Concentration (mean, median, range)	Reference
Fukuoka Prefecture 2002–5	242 Yusho patients, 74 Yusho-suspected persons in 2004, and 237 Yusho patients and 114 Yusho-suspected persons in 2005	Blood/serum	PCB-77, PCB-81, PCB-126, PCB-169	Yusho patients: 12.3, 11.7, 10.6, and 11.0 pg TEQ/g lipid in 2002, 2003, 2004, and 2005, respectively Yusho-suspected persons: 10.0, 8.3, 8.3, and 10.5 pg TEQ/g lipid in 2002, 2003, 2004, and 2005, respectively	Todaka et al. (2007b)
Japan 2001–3	359 Yusho patients	Blood/serum	PCBs 81, 77, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189	3.14 ng/g blood	Imamura et al. (2007)
Fukuoka Prefecture 2004–7	242, 237, 300, and 96 Yusho patients from 2004 to 2007, respectively, and 74, 113, 125, and 148 Yusho-suspected persons, respectively	Blood/serum	Concentrations of 64 PCB congeners: TriCB-(28, 29), TetraCB-(44, 47/48, 49, 52/69, 56/60, 63, 66, 70, 71, 74), PentaCB-(85, 87, 92, 93/95/98, 99, 101, 105, 107/108, 110, 114, 117, 118, 123), HexaCB-(128, 130, 132, 134, 135, 137, 138, 139, 141, 146, 151, 153, 156, 157, 163/164, 167), HeptaCB-(170, 172, 177, 178, 179, 180, 181, 182/187, 183, 189, 191), OctaCB-(194, 195, 196/203, 198/201, 200, 202, 205), NonaCB-(206, 207, 208), DecaCB-209	Yusho patients: 2004, 645 (40–3032) ng/g lipid; 2005, 760 (40–4723) ng/g lipid; 2006, 667 (74–2432) ng/g lipid; and 2007, 510 (51–2252) ng/g lipid Yusho-suspected persons: 2004, 355 (20–1418) ng/g lipid; 2005, 490 (64–4055) ng/g lipid; 2006, 397 (18–1850) ng/g lipid; and 440 (19–2183) ng/g lipid	Todaka et al. (2009a, b)
Fukuoka Prefecture 2002–8	26 pairs of Yusho mothers and their children (19 mothers, 26 children)	Blood/serum	PCB-77, PCB-81, PCB-126, PCB-169	In the formula-fed group: 12.65 pg TEQ/g lipid for the mothers, and 3.85 pg TEQ/g lipid for the children In the breast-fed group: 10.64 pg TEQ/g lipid for the mothers; and 3.27 pg TEQ/g lipid for the children	Tsukimori et al. (2011)
Japan [Period not specified]	27 Yusho patients	Blood/serum	Hydroxylated PCBs (4-OH-CB109, 4-OH-CB146 + 3-OH-CB153, 4-OH-CB187, 4'-OH-CB172)	Total mean (range), 687 (95–1740) pg/g ww Range of the major hydroxylated PCB metabolites: 4-OH-CB187 (54–906 pg/g ww), 4-OH-CB146 +3-OH-CB153 (32–527 pg/g ww), 4-OH-CB109 (ND–229 pg/g ww) and 4'-OH-CB172 (ND–143 pg/g ww).	Tobiishi et al. (2011)
Japan 1968–2006 (the time of delivery of Yusho descendants)	64 Yusho mothers and 117 descendants (10 with FYD and 107 without FYD)	Maternal blood/serum	DL-PCBs (77, 81, 126, 169)	Black baby group, 57.6 pg TEQ/g lipid Non-black baby group, 31.8 pg TEQ/g lipid	Tsukimori et al. (2012)

Table 1.30 (continued)

Region Period	Subjects/ participants	Sample	PCB measured	Concentration (mean, median, range)	Reference
Umbilical cord					
Japan Yusho victims (1968–2000)	11 samples from 6 Yusho babies	Preserved umbilical cord	DL-PCBs (77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)	6500 (130–11 000) pg/g in three designated patients 580 (130–1400) pg/g in eight suspected patients	Aozasa et al. (2008)
Fukuoka and Nagasaki prefectures Born 1970–3	7 babies born to Yusho mothers	Preserved umbilical cord	DL-PCBs (77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)	0.3 pg TEQ/g dw	Nagayama et al. (2010)

dw, dry weight; FYD, fetal Yusho disease; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; TEQ, toxic equivalent; ww, wet weight

Table 1.31 PCB concentrations in biological samples from Yucheng patients, Taichung County, Taiwan, China

Date of study	Patients	Sample	PCB measured	Concentration (mean, median, range)	Reference
1979–81	Children (n = 113)	Blood	PCBs	39 000 pg/g	Kashimoto *et al.* (1985)
1992	Mothers (n = 56)	Adipose tissue		2820 ± 300 (SE) ng/g	Guo *et al.* (1997)
1994–6	Adults (n = 42)	Sebum Blood	Dioxin-like PCBs	868.6 pg/g 714.4 pg/g	Iida *et al.* (1999)
1994	Adults (n = 414)	Serum	NR	1500 ng/g lipid (PCB-138 represented 29% of all measured PCBs)	Lung *et al.* (2005)
1994–5	Adults (n = 41)	Blood	NR	2468 ng/g lipid (13.3 ng/g sample) 133 pg/g (PCB TEQ in men) 127 pg/g (PCB TEQ in women)	Hsu *et al.* (2005) Lambert *et al.* (2006)

NR, not reported; PCB, polychlorinated biphenyl; SE, standard error; TEQ, toxic equivalent

from rural areas having the lowest levels of PCBs. PCB-138 and PCB-153 were found in the blood of mothers from all of the 61 sites studied at geometric mean concentrations of 3.56 and 3.2 ng/g lipid, respectively. Ahmed *et al.* (2002) reported the sum concentration of 29 congeners in blood from Egyptian women to be 61.9 ng/g. Weiss *et al.* (2006) reported concentrations of PCB-153 in infertile women in the United Republic of Tanzania to be 0.17 µg/kg. Sum PCB concentrations in serum samples from Bizerte, Tunisia, ranged from 37.5 to 284.6 ng/g lipid, with mean and median value of 136.1 ng/g lipid and 123.2 ng/g lipid, respectively. The PCB profile consisted mainly of persistent congeners such as PCB-138, PCB-153, and PCB-180 (82.7% of the sum of PCBs). PCB concentrations were significantly higher in men ($P < 0.05$) than in women (Ben Hassine *et al.*, 2014).

(b) Human milk

Due to its high fat content, human milk can accumulate large amounts of PCBs, thus making it an ideal matrix for the determination of concentrations of PCBs and other lipophilic compounds, and can be sampled using non-invasive techniques. In addition, human milk represents a good indicator of the body burden of lipophilic non-metabolized PCBs, since fat is mobilized for the production of milk during lactation. Animal studies and mass balance studies for humans have revealed that large amounts of PCBs can be eliminated through lactation (Lindell, 2012). Data are summarized in Table 1.32.

(i) Global assessment

The transfer of PCBs from mother to infants via breast milk is an important source of exposure, and several factors (including maternal residence, age, and parity) can potentially affect levels of contaminants in breast milk. Because of the importance of breastfeeding for infants, contamination of human milk is of specific public concern.

The Stockholm Convention on Persistent Organic Pollutants (POPs) is a guidance document, the objective of which is to document the effectiveness of the implementation of the obligations under the Convention. The World Health Organization (WHO) introduced worldwide measurement campaigns to determine the exposure of infants to dioxin-like PCBs (UNEP, 2012).

Table 1.32 PCB concentrations in human milk, by country

Country, population	PCBs (WHO-TEQ pg/g fat)			Sum indicator PCBs (ng/g fat)[a]			Reference
	Mean	Median	Range	Mean	Median	Range	
Europe, 1992–2003							
Czech Republic	–	15.24	14.32–28.5	–	502	496–1009	Van Leeuwen & Malisch (2002)
Germany	–	13.67	12.8–14.3	–	220	188–238	Ulaszewska *et al.* (2011)
	DL-PCBs: 12.60 (in Duisburg) 6.31 (in Munich)	–	–	–	–	–	
Greece	–	6.56 DL-PCBs	–	–	–	–	Costopoulou *et al.* (2006)
Italy (Milan, Rome, Venice)	–	16.29	11.02–19.33	–	253	195–323	Weiss *et al.* (2003), Ingelido *et al.* (2007), Abballe *et al.* (2008)
	–	–	DL-PCBs, 6.02–19.21 pg WHO_{2005}-TEQ/g lipid	–	–	–	
Norway	–	8.9	6.56–9.61	–	119	106–132	Polder *et al.* (2008)
Spain	–	–	–		(Sum of PCB-138, PCB-153, PCB-180) × 1.7: 1355 (in 1994) 653 (in 2000)	–	Cerná *et al.* (2008)
Spain	–	–	–	–	241	162–467	Schuhmacher *et al.* (2009)
	DL-PCBs, 4.8 pg WHO_{2005} TEQ/g lipid	–	–	–	–	–	
Sweden	–	9.71	–	–	146	–	Norén & Meironyté (2000)
North America							
Canada, *n* = 86 women eating fish from Lake Ontario	–	–	153 (50th percentile)	–	–	–	Stewart *et al.* (2003)
Western Canada, *n* = 47 women	–	38.20	–	–	–	–	Jarrell *et al.* (2005)
Canada, Northern Quebec, Inuit women from Nunavik	–	385.0 ± 1.9 SD	75.7–1915.8	–	–	–	Muckle *et al.* (2001)
USA, North Carolina, *n* = 331 women	–	77	9–708	–	–	–	Pan *et al.* (2010)

Table 1.32 (continued)

Country, population	PCBs (WHO-TEQ pg/g fat)			Sum indicator PCBs (ng/g fat)[a]			Reference
	Mean	Median	Range	Mean	Median	Range	
South and Central America							
Brazil, Rio de Janeiro, *n* = 40 mothers	9.7	–	150	–	–	–	Paumgartten *et al.* (2000)
Africa							
Ghana, *n* = 67 mothers	62	–	15–160	–	–	–	Asante *et al.* (2011)
South Africa, Limpopo Provence	10	–	–	–	–	–	Darnerud *et al.* (2011)
Tunisia	180	–	–	–	–	–	Ennaceur *et al.* (2008)
Zimbabwe	26	–	–	–	–	–	Chikuni *et al.* (1997)
Asia							
Japan	1.30×10^3 (in 1972) 1.51×10^3 (in 1974) 0.20×10^3 (in 1998)						Environment Agency of Japan (1999)
China, *n* = 1237				–	–	–	Li *et al.* (2009)
Total TEQ	5.42	5.11	Upper bound, 2.59–9.92	–	–	–	
Estimated dietary intake of PCDD/PCDF + DL-PCBs in infants	28.0 pg TEQ/kg bw per day	–	14.2–48.6 pg TEQ/kg bw per day	–	–	–	

[a] Indicator PCBs are PCBs 28, 52, 101, 138, 153 and 180

DL-PCB, dioxin-like polychlorinated biphenyl; PCB, polychlorinated biphenyl; TEQ, toxic equivalent

The evaluation of the Stockholm Convention has been applied (with slight changes) for five rounds of the UNEP/WHO survey. Often, human milk from primiparae mothers (for detail, see UNEP, 2012) is preferred to human blood, since sampling is non-invasive and PCBs are easier to detect (due to the higher lipid content of milk). It should be noted that for global assessment, the concentrations of dioxin-like PCBs (DL-PCBs) on a TEQ basis for the last three rounds of the UNEP/WHO survey on mothers' milk may be lower by 30% (range, 2–60%) if WHO toxic equivalency factors (TEFs) for 2005 (WHO_{2005}-TEF) are applied, rather than those for 1998 (WHO_{1998}-TEF). International chemical assessments report that the average concentration of PCBs in human milk fat ranges from 0.5 to 4 μg/g (IPCS, 2003). For the sum of PCB_6, the median is between 10.8–30.7 ng/g lipid, and maxima are between 37.1–65.8 ng/g lipid. Overall, the UNEP/WHO survey showed a correlation between maternal age and concentrations of DL-PCBs in breast milk, and lower concentrations of PCBs in breast milk of multiparous women when compared with primiparous women.

(ii) Americas

The mean concentration of PCBs in whole breast milk in Canadian women steadily increased from 6 μg/kg in 1970 to 12 μg/kg in 1975, and to 26 μg/kg in 1982, before declining to 6 μg/kg in 1986 (IPCS, 2003).

Recent data on concentrations of PCDD/PCDFs and DL-PCBs in human milk from South America were reported only for Brazil (Paumgartten *et al.*, 2000).

(iii) Europe

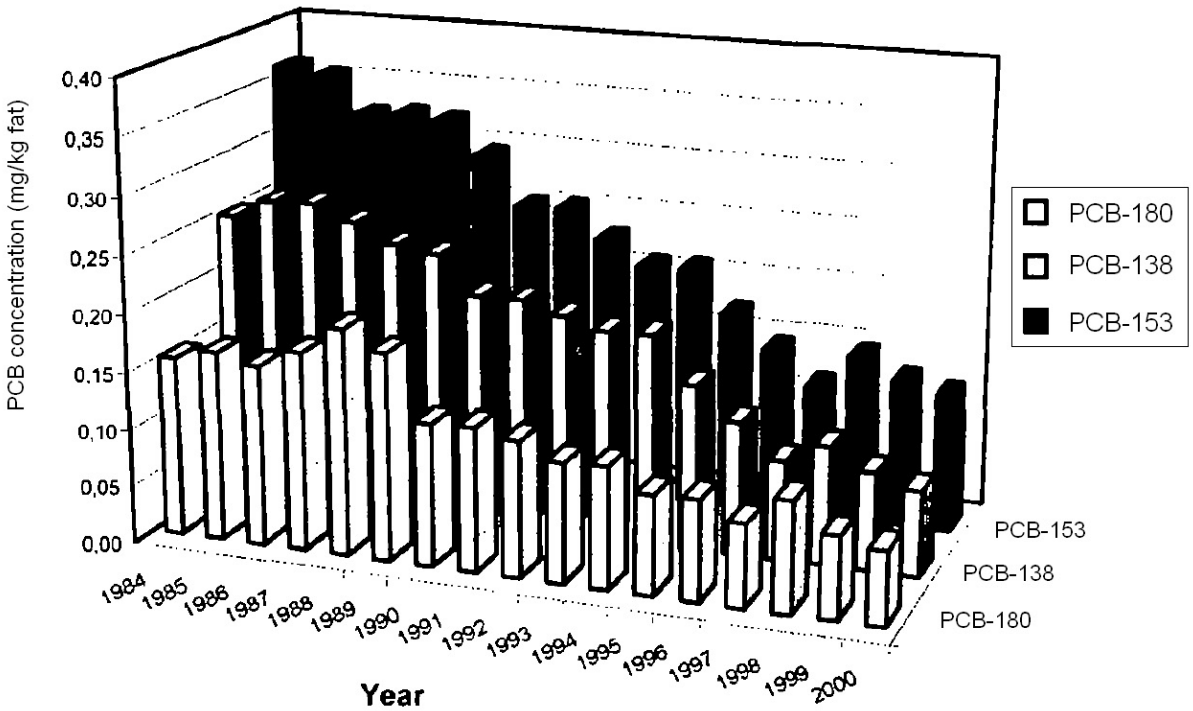
In Europe, concentrations of DL-PCBs (on a TEQ basis) and PCB indicators in human milk are considerably higher than in other regions of the world, a legacy from past exposures. For the sum of PCB_6, the median of 115.3 ng/g lipid is between 3.8 times and 10.7 times higher than in other regions of the world, and maximum concentrations are up to 14.9 times higher (IPCS, 2003). However, a WHO survey identified a decrease in WHO-TEQ PCDD/PCDF and PCB concentrations in human milk over the last decade (Van Leeuwen *et al.*, 2002). It was assumed that this decrease was the result of the ban of PCB use in open systems, and the strict regulations on the use of PCBs and on their disposal in closed systems.

Norén & Meironyté (referenced in IPCS, 2003) reported a steady decrease (from 910 to 324 ng/g lipid) in total PCB concentrations in the breast milk of Swedish women between 1967 and 1997. A declining trend could be observed for the sum of the PCB_6 in Germany, and mean values for the congeners PCB-138, PCB-153 and PCB-180 were approximately 60–70% lower in 2000 than in 1984 (Fürst, 2001; Fig. 1.8). An approximately 74% decrease in DL-PCB concentrations during the last decade was reported in Italy (Di Domenico & Turrio Baldassarri, 1990; Weiss *et al.*, 2003; Abballe *et al.*, 2008). Analyses of milk samples from the Czech Republic also revealed a decline in median concentrations between 1994 and 2000, the strongest decrease being observed between 1994 and 1997 (Cerná *et al.*, 2008). Nevertheless, it should be noted that concentrations in areas with heavy contamination did not show a significant decline in exposure over the past 10 years.

(iv) Asia

In Japan, a time-trend study showed that average PCB concentrations in human milk increased from 1.3 ng/g in 1972 to a peak of 1.5 ng/g in 1974, and then decreased by about 13% in 1998 (Environment Agency of Japan, 1999). In contrast, daily intake of PCBs from breast milk was estimated to decrease from 22.3 μg/g to 0.31 μg/g during this same period. [This trend reflects a change in PCB concentrations in food, due to both a decrease in contamination and more dependence on imported foods, which were less

Fig. 1.8 PCB concentrations in human milk in Germany, 1984–2000



From Fürst (2001)
PCB, polychlorinated biphenyl

contaminated than domestic foods (IPCS, 2003), and is consistent with the observed decline in PCB concentrations in the environment and in human tissues.]

In China, a national investigation of individuals in 12 provinces representing approximately 50% of the total Chinese population reported PCDD/PCDF-TEQ and total-TEQ in human milk from rural areas to be lower than those from urban areas (Li *et al.*, 2009). Positive correlations were found between total-TEQ in human milk and the consumption of aquatic food and meat.

PCB levels in breast milk samples from women in Asia are summarized in Table 1.29 and Table 1.30.

(c) Adipose tissue

(i) North America

Lordo *et al.* (1996) reported PCB concentrations (sum of tetra- to octochlorobiphenyls) in pooled adipose tissue to be 672 ng/g in 1986, compared with 407 ng/g in 1982, and 508 ng/g in 1984. Stellman *et al.* (1998) reported a total PCB concentration of 267 ng/g in breast adipose tissue of healthy women from Long Island, New York. An approximation of Aroclor 1260 [summed concentrations of PCB-138 and PCB-153 multiplied by 5.2] measured in breast adipose tissue, was reported to be 870 ng/g (Aronson *et al.*, 2000). Muscat *et al.* (2003) measured PCB concentrations (sum of 14 congeners) in breast adipose

tissue in women without metastatic breast cancer to be 361 ± 235.9 ng/g and 395.4 ± 279.3 ng/g, in women who did not have recurrence and women who did have recurrence, respectively.

(ii) Europe

The results of a study conducted in 1993–94 suggested that concentrations of PCBs in adipose tissue are the best indicator of long-term exposure or of total body burden of PCBs, compared with human milk or blood (Kocan *et al.*, 1994).

PCB concentrations in adipose tissue of the general population in industrialized countries vary very widely, ranging from < 1000 to 5000 ng/g fat (Falandysz *et al.*, 1994; Holoubek *et al.*, 1995, 2001b). In a comparative study in Europe (Van Bavel *et al.*, 2003), PCB concentrations in the population in Sweden were one third (mean, 661.9 ng/g fat; range, 247.2–1651.2 ng/g fat; Σ37 PCBs) of those in the Hungarian samples.

(iii) South and Central America

Breast adipose tissue in 76 women from an agricultural region of north-eastern Argentina contained eight PCBs at very low levels (only 1.3% above detection limits), but high levels of *p,p*-dichlorodiphenyldichloroethane (DDE) and other pesticides (Muñoz-de-Toro *et al.*, 2006).

The sum of four PCB congeners in children from Nicaragua was 530 ng/g lipid weight (2.0 ng/g wet weight) in those living and working near a waste-disposal site and eating fish from contaminated Lake Managua, 230 ng/g lipid weight (0.9 ng/g wet weight) in those living nearby but not working at the waste site and not eating fish, and 160 ng/g lipid weight (0.6 ng/g wet weight) in those living at a distance from the waste site and not eating fish (Cuadra *et al.*, 2006).

(iv) Asia

PCB concentrations in adipose tissue were reported from Yusho and Yucheng patients (see Table 1.30 and Table 1.31).

(v) Adipose versus serum measurements

Arrebola *et al.* (2012a, b) measured concentrations of three PCB congeners in serum and adipose tissue in adults from Bolivia. PCB-138 had median concentrations of 0.2 ng/mL in serum [33.7 ng/g lipid] and 84 ng/g in adipose tissue [105 ng/g lipid]. The median values for PCB-153 was 0.3 ng/mL in serum [59.0 ng/g lipid], and 52.7 ng/g in adipose tissue [65.8 ng/g lipid]. PCB-180 had median values of 0.1 ng/mL in serum [26.7 ng/g lipid] and 32.8 ng/g in adipose tissue [41.0 ng/g lipid].

(d) Umbilical cord blood, placenta, and fetal tissue

(i) North America

Stewart *et al.* (2000) reported cord blood PCB concentrations from women living along Lake Ontario and eating contaminated fish. The average cord blood PCB concentration was 0.525 ng/g wet weight [25th percentile, 0.174 ng/g wet weight; 75th percentile, 1.11 ng/g wet weight]. In plasma from umbilical cord in Inuit women from northern Canada, the geometric mean for the sum of 14 PCB congeners was 279.9 ng/g lipid (range, 70.8–1420.1 ng/g lipid) (Muckle *et al.* 2001). Dallaire *et al.* (2003) reported changes in concentrations in umbilical cord blood in this population over time, and found a 7.9% annual decrease between 1994 and 2000. Choi *et al.* (2006) measured 51 congeners in cord blood from women living near a PCB-contaminated site in Massachusetts, and reported a geometric mean of 0.40 ng/g (range, 0.068–18.14), with no consistent relationship with residential distance from the waste site. Consumption of meat and local dairy products (but not fish) were associated with higher cord blood PCB concentrations.

In women from New York state, Schecter *et al.* (1998) reported the concentration of three dioxin-like PCBs to be 18.2 pg/g lipid in placenta, giving a TEQ of 1.05. The concentrations of 14 single PCB congeners in plasma from Inuit

women from Nunavik and southern Quebec were highly correlated with those in placenta (Pearson's $r = 0.77–0.97$; $P < 0.001$), and concentrations in Inuit women were on average four times higher than in women from southern Quebec (Pereg *et al.*, 2002). Doucet *et al.* (2009) analysed placenta from Canadian women having elective abortions in 1998–2006 and reported annual average total PCB concentrations ranging from 7 to 70 ng/g lipid, with no clear time trend.

(ii) Europe

Koopman-Esseboom *et al.* (1994) used the concentrations of four congeners (PCB-118, PCB-138, PCB-153, and PCB-180), as measured in umbilical cord blood and in breast milk, as indicators of exposure of the developing fetus and breastfed infant. For these congeners, the correlation coefficients between maternal plasma, cord plasma and human milk were highly significant.

Soechitram *et al.* (2004) analysed PCBs (PCB-118, PCB-138, PCB-146, PCB-153, PCB-156, PCB-180) and hydroxylated metabolites of PCBs (PCB-107, PCB-136, PCB-146, PCB-153, PCB-172, PCB-187) in samples of maternal plasma and corresponding cord blood in the Netherlands. The calculated ratio for cord versus maternal blood was 1.28 ± 0.56 for PCBs and 2.11 ± 1.33 for hydroxylated PCBs, expressed per gram of lipid. A significant correlation between the respective maternal and cord concentrations for both PCBs and hydroxylated PCBs was found. The results indicated that approximately 50% and 30% of hydroxylated PCBs and PCBs, respectively, was transferred across the placenta to the fetus.

(e) Hair

(i) North America

Altshul *et al.* (2004) reported median PCB concentrations (sum of 57 congeners) in hair of 2640 ng/g fat (range, 1180–3620 ng/g fat) in a population of students in Boston, USA. Washing hair with shampoo decreased concentrations of PCBs by 25–33% on average, and up to 62% for less chlorinated congeners. [The Working Group considered that the analytical method was reliable and reproducible.] The concentrations of PCBs in hair were higher than in serum. Correlation between concentrations in hair and blood was moderate for the more persistent PCB congeners, with no or little correlation for the other congeners.

(ii) Europe

Covaci *et al.* (2002b) assessed PCB exposure in hair samples from Greece, Romania, and Belgium. Mean PCB concentrations in samples from Belgium were up to 14 ng/g hair, while concentrations in samples from Greece were about three times lower. Similar ratios of PCB-153 over total PCBs were found for all three countries.

(iii) Asia

One study measured PCB concentrations in the hair of pregnant women in various cities in the Islamic Republic of Iran (see Table 1.29).

1.5 Occupational exposure to PCBs

In 1978, an estimated 12 000 persons in the USA were exposed occupationally to PCBs (Lloyd *et al.*, 1976; NIOSH, 1977). Since the previous IARC evaluations of PCBs (IARC, 1978, 1987), occupational exposures to PCBs have changed, since most industrial countries have banned or partially banned their use. Nevertheless, the earlier references cited previously have been incorporated in the present monograph.

Earlier occupational exposures to PCBs occurred during PCB manufacture, capacitor and transformer manufacture and repair, production of carbonless copy paper, and accidental releases from these processes. More recent occupational exposures to PCB usually occur through PCB emissions via waste incineration, fires, and waste recycling.

1.5.1 PCB manufacture

The few available studies of occupational exposure among PCB-manufacturing workers have been performed in France, Italy, Japan, Poland and the USA. Workers' exposures during PCB manufacture have been mentioned since 1936 (Jones & Alden, 1936); air PCB concentrations ranged from 26 to 163 μg/m³. Evidence of extensive exposures was available from two larger clinical studies in Slovakia in which workers' blood concentrations were measured at 1160–9600 ng/g lipid (n = 242) (Langer *et al.*, 1997), and 4905–6540 ng/g lipid (n = 240) (Langer *et al.*, 2002). These workers had been employed at the plant for at least 5 years, but no information was given regarding the type of activities that they had performed.

1.5.2 Capacitor manufacture

Before PCBs were banned, capacitor manufacturers filled (impregnated) casings with wound paper and foil/plastic with the PCB-containing oil before the top was fastened (crimped, sealed, soldered). PCB exposure (probably via the dermal route) occurred during filling: the capacitors were either flood-filled or manually filled, resulting in spills and worker exposures. The brand of PCB oil used differed geographically (Aroclors were used in the USA, Pyralene/Phenochlor in Sweden and Italy) and temporally (the percentage chlorination was reduced, e.g there was a switch from Aroclor 1254, with 54% chlorination, to Aroclor 1242, with 42% chlorination.

Other chemical exposures in capacitor manufacturing were possible, such as from other impregnation oils (e.g. mineral oils), degreasing agents such as trichloroethylene (Brown & Jones, 1981; Bertazzi *et al.*, 1987), dibenzofurans (Gustavsson *et al.*, 1986), chlorinated naphthalenes, lead solder, epoxies, and methyl ethyl ketone (MEK) (Mallin *et al.*, 2004; Persky *et al.*, 2012). Ageing capacitors can from time to time explode [due to the physical stress of metal ageing], thus further exposing workers.

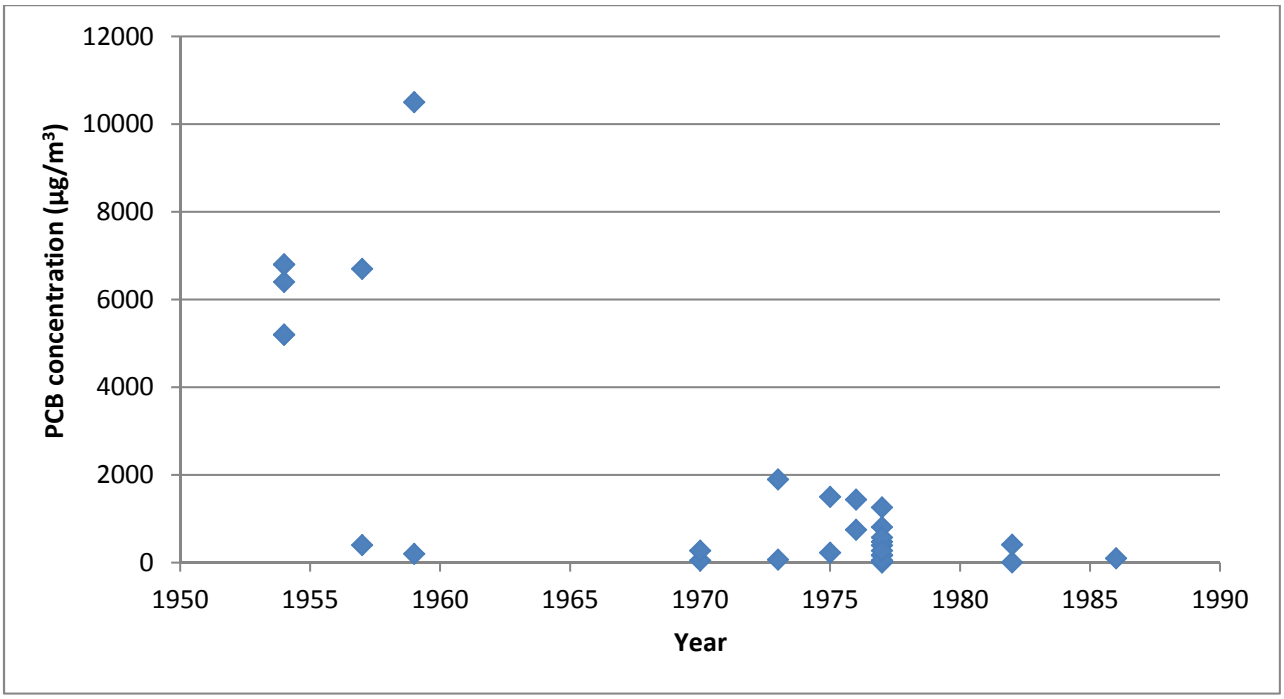
Fig. 1.9 shows ranges of air PCB concentrations in capacitor-manufacturing sites (Ouw *et al.*, 1976; Brown & Jones, 1981; Bertazzi *et al.*, 1982; Fischbein *et al.*, 1982; Lawton *et al.*, 1985; Gustavsson *et al.*, 1986). The earlier concentrations (measured in the 1950s–1960s) were highest (Bertazzi *et al.*, 1982), and decreased in later years.

In the 1950s, maximum PCB concentrations in workroom air in several plants in the USA (Massachusetts) were reported to be 200–10 500 μg/m³ (Elkins, 1959). No details on the number of plants surveyed, nor the number of samples collected, or the work performed in the plants were given, but four different jobs were surveyed: for impregnating with PCBs, average air concentrations ranged from 200 to 5800 μg/m³; for soldering, 800 μg/m³; mixing oil, 600 μg/m³, and regulator filling, 100 μg/m³. No toxic effects were noted at these concentrations; however, it was noted that air PCB concentrations of > 10 000 μg/m³ were "unbearably irritating." This is contrary to a report in a Japanese capacitor-manufacturing plant where a dermatitis outbreak occurred when air PCB concentrations reached 100 μg/m³ (Meigs *et al.*, 1954). Air PCB concentrations between 1953 and 1957 in a Japanese capacitor-manufacturing factory ranged from 400 to 6700 μg/m³ (NIEHS, 1976).

Ouw *et al.* (1976) reported that workers in the electrical industry in Australia were exposed to Aroclor 1242 at air concentrations of 320–2220 μg/m³, with a mean of 1270 μg/m³; and were found to have PCB blood concentrations of approximately 0.4 g/kg bw. Contact with PCBs was primarily via the skin.

Brown & Jones (1981) measured air concentrations of Aroclor 1016 in two plants in the USA (New York and Massachusetts) plants in 1977. The time-weighted averages (TWA) were different for the two plants, with air concentrations at the New York plant being lower than at the Massachusetts

Fig. 1.9 Air PCB concentrations in capacitor manufacturing plants (µg/m³) by year



Compiled by the Working Group using data from Ouw *et al.* (1976), Brown & Jones (1981), Bertazzi *et al.* (1982), Fischbein *et al.* (1982), Lawton *et al.*(1985) and Gustavsson *et al.*(1986)
PCB, polychlorinated biphenyl

plant. For the New York plant, PCB concentrations in personal air samples ranged from 24 to 393 µg/m³ (n = 28), and in area air samples from 3 to 476 µg/m³ (n = 19). For the Massachusetts plant, PCB concentrations in personal air samples ranged from 170 to 1260 µg/m³ (n = 29), and in area air samples from 50 to 810 µg/m³ (n = 25). Air PCB concentrations (TWA) were extremely high during capacitor impregnation (New York: 160 µg/m³, Massachusetts: 850 µg/m³), degreasing (Massachusetts; 1260 µg/m³), and sealing/soldering (New York: 393 µg/m³, Massachusetts: 720 and 1060 µg/m³). Capacitors that failed were sent for repair where they were re-opened and manually drained. Repair workers' PCB exposures were measured as 298 µg/m³ (recovery), and 50 µg/m³ (repair) in the New York plant. [These workers would also have had extensive dermal exposures, which were not assessed.]

Eight studies have reported PCB concentrations in workers' blood in Australia, Finland, Italy, Germany, and the USA (Karppanen & Kolho, 1972; Ouw *et al.*, 1976; Maroni *et al.*, 1981a; Bertazzi *et al.*, 1982; Acquavella *et al.*, 1986; Wolff *et al.*, 1992; Kannan *et al.*, 1994; Seegal *et al.*, 2011; Persky *et al.*, 2012). The reporting of PCB blood concentrations was not uniform, which hindered comparison across studies.

Karppanen & Kolho (1972) compared blood PCB concentrations in workers in a capacitor factory in Finland where Aroclor 1242 had been used as the impregnating fluid: the groups comprised laboratory workers handling PCBs (n = 6), impregnation workers (n = 11) employed for 4 years, and a control group (n = 9) that had never been professionally exposed to PCBs. Blood PCB concentrations were approximately 50 times greater in impregnation workers (0.07–1.9 µg/g)

than in the control group (0.003–0.012 μg/g), and were also higher in laboratory workers (0.036–0.062 μg/g) than in the controls. The pattern of PCB congeners in the exposed workers differed markedly from that of the PCBs actually used. More highly chlorinated PCBs persisted in the blood, while the less chlorinated PCBs contained in Aroclor 1242 had been eliminated from the body. [Consequently, the total PCB intake must have been higher than that reflected by the levels detected in blood.]

Total serum PCB concentrations have been reported to be 18.2 ppb (Acquavella *et al.*, 1986) in a clinical survey among 205 workers at a capacitor-manufacturing plant in the USA. This mean value represented workers (n = 205) with (39%) and without (61%) potential for PCB exposure in their jobs. [The Working Group noted that PCB concentrations were not reported separately for workers with and without occupational PCB exposure.] Log serum PCB concentrations were found to be significantly correlated with duration of employment, age, cumulative occupational exposure, and fish and wine consumption, as confirmed by multiple linear regression.

In a study of mortality in Italy (Bertazzi *et al.*, 1982), workers in the autoclave room were exposed to air PCB concentrations of 5200–6800 μg/m^3 in 1954 (n = 3), and 48–275 μg/m^3 in 1977 (n = 9). Eighteen workplace surface-wipe samples showed extensive PCB contamination (0.2–159 μg/cm^2), as did nine hand-wipe samples (0.3–9.2 μg/cm^2). Workers' serum PCB concentrations were reported by type of PCBs: for highly chlorinated PCBs (54% chlorination) (n = 67), the mean was 230.5 ppb (SD, 174.5), while for less chlorinated PCBs (42% chlorination) (n = 67) the mean was 114.1 ppb (SD, 79.6). In a later study (Bertazzi *et al.*, 1987), the corresponding values were 202.8 ppb (SD, 111.7; n = 37) and 42.9 ppb (SD, 34.7; n = 37), respectively.

Wolff *et al.* (1992) studied PCB blood concentrations in capacitor workers in 1976 and 1979 in the USA. For the first sampling year, the mean concentration of the less chlorinated PCBs (di-, tri-, and tetrachlorobiphenyls) was 55 ng/mL (range, 6–2257 ng/mL), and for the latter year was 41 ng/mL (range, 6–350 ng/mL). Mean concentrations of highly chlorinated PCBs were 10 ng/mL (range, 1–308 ng/mL) in 1976, and 13 ng/mL (range, 2–350 ng/mL) in 1979. These capacitor workers (n = 60) were also surveyed by the National Institute for Occupational Health and Safety in 1977 (NIOSH, 1977), when the following blood PCB concentrations were reported as follows: less chlorinated PCBs (quantified as Aroclor 1242), 2–3300 ppb (ng/mL), and more highly chlorinated PCBs (quantified as Aroclor 1254), 5–250 ng/mL.

About 30 years later (in 2003–2006), Seegal *et al.* (2011) measured blood concentrations of individual PCB congeners in some of these former capacitor workers, and found that concentrations had dropped statistically significantly: mean concentration of less chlorinated PCBs (PCBs 28, 56, 66, 74, 99, 101) was 2.84 ng/g or 0.45 μg/g lipid in men, and 2.29 ng/g or 0.34 μg/g in women; mean concentration of highly chlorinated PCBs (PCBs 105, 118, 138, 146, 153, 156, 167, 170, 172, 174, 177, 178, 180, 183, 187, 199, 203) was 4.09 ng/g or 0.65 μg/g lipid in men, and 3.21 ng/g or 0.47 μg/g lipid in women; and total PCB concentration was 7.47 ng/g or 1.19 μg/g lipid in men, and 5.81 ng/g or 0.86 μg/g lipid in women.

Maroni *et al.* (1981a) carried out a study in two Italian electrical-capacitor manufacturing plants using PCBs as a dielectric fluid. Plant A produced electric capacitors filled with a mixture of mineral oils and PCBs. PCBs with 54% chlorination were used from 1949 to 1965, and subsequently replaced with Pyralene 3010 with 42% chlorination. The power-capacitor casings were filled with PCBs in autoclaves, and were manually removed when cooled from 70 °C to 40 °C before they were welded, tested, and finished externally. Electric "filters" (small capacitor systems used in electrical household appliances)

were impregnated with PCBs. Plant B performed short-circuit testing of high-power capacitors filled with Apirolio, a PCB mixture with 42% chlorination. Stress-testing the capacitors often included explosions. Airborne PCBs were mainly trichlorobiphenyls and concentrations ranged from 48 μg/m^3 (filter operations) to 275 μg/m^3 (power-capacitor manufacturing). Surface-wipe samples showed both tri- and pentachlorobiphenyl mixtures, with the highest amounts being found on the capacitor basket rolling carrier: trichlorobiphenyls, 127 mg; and pentachlorobiphenyls, 15 mg. Plant A employed 67 workers (40 women and 27 men): 48 were currently employed in the capacitor-manufacturing departments, 16 had been employed there for at least 6 months before the beginning of the study, and 3 had always been employed in other non-manufacturing departments without direct exposure to PCBs. PCB recovery from the palms of the hands of power-capacitor workers (plant A) showed total PCB (tri- and pentachlorinated biphenyls) skin-surface concentrations to be 4–28 μg/cm^2. Mean (± SD) blood PCB concentrations differed between current (377 ± 190 μg/kg) and past exposed workers (292 ± 161 μg/kg); workers with occasional exposure had the lowest mean total PCB exposures (110 ± 31 μg/kg). Blood PCB concentrations by job performed were highest for welders (1259 μg/kg), followed by impregnation workers (556 ± 337 μg/kg), assembly of capacitors (406 ± 173 μg/kg), and finally assembly of filters (246 ± 130 μg/kg). The blood PCB concentrations were not correlated with duration of exposure, but with the percentage ratio of hours per year spent with direct exposure to PCBs. Plant B included 13 workers (all men) exposed to PCBs during handling of the capacitors contaminated with Apirolio, dispersed from explosions sometimes caused by stress-testing. Blood PCB concentrations in currently exposed workers in plant B (200 ± 146 μg/kg) were between occasionally exposed (110 ± 31 μg/kg) and past exposed workers (292 ± 161 μg/kg) in plant A. Although the PCB mixture used in both plants had a chlorine content of 42%, the workers differed in their ratio of penta- to trichlorobiphenyls; plant A workers had higher concentrations of pentachlorobiphenyls than of trichlorobiphenyls, while the reverse was true in plant B workers. This difference was attributed to the heavy past exposure to highly chlorinated PCBs used until 1965 in plant A. Workers with abnormal liver findings (n = 16) had twice the concentrations of tri- (215 ± 95 μg/kg) and pentachlorobiphenyls (308 ± 306 μg/kg) compared with workers (n = 64) without abnormal liver findings (tri- and pentachlorobiphenyl concentrations were 92 ± 64 and 176 ± 108 μg/kg, respectively) (Maroni *et al.*, 1981b). Duration of exposure did not explain this observed difference.

One German capacitor-manufacturing worker was reported to have a blood PCB-169 concentration of 11 ng/g (Kannan *et al.*, 1994).

After a capacitor explosion at a Finnish paper mill, workers' (n = 15) blood PCB concentrations were 3.5–48.3 μg/L (Luotamo *et al.*, 1984). [These levels were much lower than during capacitor manufacturing itself.]

In a recent cross-sectional study, Persky *et al.* (2012) reported blood PCB concentrations separately for diseased (having diabetes) and non-diseased (without diabetes) workers. In diseased workers, the concentrations were: DL-PCBs, 2.5 ng/g; NDL-PCBs, 17.0 ng/g; estrogenic PCBs [PCB-52, 99, 101, 110, 153], 3.6 ng/g; anti-estrogenic PCBs [PCB-105, PCB-156], 3.6 ng/g; and PCB-74, 4.9; PCB-99, 1.0 ng/g; PCB-118, 1.4 ng/g; PCB-138, 2.5 ng/g; PCB-146, 0.4 ng/g; PCB-153, 2.8 ng/g; PCB-156, 0.6 ng/g; PCB-170, 0.7 ng/g; PCB-180, 1.1 ng/g; PCB-187, 0.3 ng/g; PCB-194, 0.2 ng/g; PCB-201, 0.2 ng/g; PCB-203, 0.2 ng/g; and PCB-206, 0.1 ng/g. In non-diseased workers, the concentrations were: DL-PCBs, 0.4 ng/g; NDL-PCBs, 4.3 ng/g; estrogenic PCBs, 1.0 ng/g; anti-estrogenic PCBs, 0.1 ng/g; PCB-74, ng/g; 0.8, PCB-99; 0.3 ng/g; PCB-118, 0.2 ng/g; PCB-138, 0.6 ng/g; PCB-146, 0.1 ng/g; PCB-153,

0.8 ng/g; PCB-156, 0.1 ng/g; PCB-170, 0.2 ng/g; PCB-180, 0.4 ng/g; PCB-187, 0.1 ng/g; PCB-194, 0.1 ng/g; PCB-201, 0.1 ng/g; PCB-203, 0.1 ng/g; and PCB-206, 0.04 ng/g.

1.5.3 Transformer manufacture and repair

Transformer manufacture was very similar to capacitor manufacture. Transformers were filled with PCBs, but the impregnation fluid was usually diluted with other chlorinated solvents (e.g. trichlorobenzene; Greenland *et al.*, 1994), and sold under different names such as Askarel (Inerteen), Pyranol, Chlophen, Apirolio, and Derol (Kerns, 1975; Lees *et al.*, 1987; Emmett *et al.*, 1988; Kalina *et al.*, 1991; Greenland *et al.*, 1994; Yassi *et al.*, 1994; Altenkirch *et al.*, 1996; Loomis *et al.*, 1997; Caironi *et al.*, 2005).

Although air concentrations from transformer manufacture were not available, two studies reported air PCB concentrations during transformer repair in two different USA plants (Lees *et al.*, 1987; Emmett *et al.*, 1988). Work activities were sampling and testing transformer fluids for dielectric properties, topping up transformers when oil levels were low, clean-up of any spills or leaks, repair of transformers by drainage of transformer oil to replace parts, and periodic filtering of the transformer oil to upgrade its dielectric properties. Ranges of air PCB concentrations for several job tasks were reported: repair and clean-up (n = 3), 43.1–60.0 μg/m^3 and TWA, 16.7–24.0 μg/m^3; clean-up of PCB leakage (n = 3), 0.1–3.1 μg/m^3 and TWA, 0.01–0.4 μg/m^3; and secondary oil leak repair and clean-up (n = 15), 2.1–17.1 and TWA, 0.7–12.4 μg/m^3 (Emmett *et al.*, 1988). Other job tasks for which concentrations were reported were draining and pumping transformer oil (n = 9), 1.1 μg/m^3; transformer repair (n = 15), 1.2 μg/m^3; network repair (n = 6), 0.5 μg/m^3; topping-up transformer oil (n = 3), 0.5 μg/m^3; explosion spill clean-up (n = 16), 1.7 μg/m^3; and filtering transformer oil (n = 6), 6.1 μg/m^3 (Lees *et al.*, 1987). Transformer-repair activities included handling transformer parts that were wet with transformer fluid without protective gloves, resulting in extensive dermal exposure. In one case, a maintenance transformer worker involved in cleaning up transformer fluid spills daily had a plasma PCB concentration of 250 μg/L (Tröster *et al.*, 1991). [This value is comparable to highly exposed capacitor-manufacturing workers.]

1.5.4 Waste incineration of PCB materials

Ten studies from seven countries (USA, Germany, Spain, Japan, the Republic of Korea, Belgium, and Poland) reported PCB exposures during waste incineration of PCB materials (Colucci *et al.*, 1973; Angerer *et al.*, 1992; Wrbitzky *et al.*, 1995; Gonzalez *et al.*, 2000; Kitamura *et al.*, 2000; Domingo *et al.*, 2001; Raemdonck *et al.*, 2006; Mari *et al.*, 2009; Park *et al.*, 2009). The PCB congeners frequently reported in this industry were PCB-28, PCB-138, PCB-153, and PCB-180. The distribution of PCB congeners in plasma depended on the type of waste material, the furnace (age and type), and the workers' activities. During burning of waste in a waste-incinerating plant, heat from combustion gases is recuperated in a cauldron to produce electricity. PCBs are, together with dioxins, produced by synthesis from organic substances and chorine during this and subsequent cooling-down processes. PCBs (with dioxins) precipitate onto particulate matter (fly ash) and are trapped in the filter (Raemdonck *et al.*, 2006).

Exposed refuse workers (n = 37) in the USA had a median plasma PCB concentration of 2.6 ppb (maximum, 14.1 ppb) (Colucci *et al.*, 1973). [No methods were reported.] Hazardous-waste workers (n = 53) in Germany had a mean plasma PCB concentration of 6.33 μg/L calculated as the sum of PCB congeners PCB-138 (1.86 μg/L) + PCB-153 (2.83 μg/L) + PCB-180 (1.65 μg/L), which was not significantly different

from controls (6.22 µg/L) in the same study (Angerer *et al.*, 1992).

Another study in Germany (Wrbitzky *et al.*, 1995) reported mean plasma PCB concentrations in waste-incineration workers (total PCBs, 3.10 µg/L; range, 1.59–6.89 µg/L) that were approximately half those in the previously described study (Angerer *et al.*, 1992). The total PCBs were the sum of the same PCB congeners as previously reported: PCB-138, 0.95 µg/L (range, 0.49–2.60 µg/L); PCB-153, 1.38 µg/L (range, 0.97–3.10 µg/L); PCB-180, 0.79 µg/L (range, 0.32–1.63 µg/L). Concentrations of PCB-28, PCB-52, and PCB-101 were below the limit of detection (< 0.2 µg/L). These workers operated the incinerator, control panels, electronics, waste gas and transfer stations, and maintained and cleaned boilers and furnaces. Workers employed in the central laboratory, incoming control and sampling, chemical-sorting station, waste-water purification, and mechanical workshop among other periphery jobs had blood PCB concentrations similar to those of workers in management. Concentrations in exposed workers were: total PCBs, 2.82 µg/L; range, 1.21–7.03 µg/L, and this was the sum of PCB-138 (0.87 µg/L; range, 0.24–2.35 µg/L), PCB-153 (1.22 µg/L; range, 0.27–2.83 µg/L), and PCB-180 (0.72 µg/L; range, 0.32–3.48 µg/L). Concentrations in workers in management were: total PCBs, 3.19 µg/L (1.59–7.53 µg/L); PCB-138, 0.98 µg/L (0.49–1.98 µg/L); PCB-153, 1.42 µg/L (0.67–3.37 µg/L); PCB-180, 0.80 µg/L (0.43–2.18 µg/L). [Of the six PCB congeners analysed, only these three were detected.]

Waste-incinerator workers in a plant in Spain were reported to have mean total PCB concentrations of 1.47 µg/L: as in the German study, this was the sum of congeners PCB-138 (0.36 µg/L) + PCB-153 (0.49 µg/L) + PCB-180 (0.57 µg/L) (Gonzalez *et al.*, 2000). Congeners PCB-28 and PCB-52 were not detected, and the concentration of PCB-101 was very low (0.02 µg/L). In another study in Spain, congener-specific concentrations were reported as means (and geometric means): PCB-28, 18.5 (12.9) µg/kg lipid; PCB-52, 10.4 (7.5) µg/kg lipid; PCB-101, 9.0 (7.1) µg/kg lipid; PCB-138, 151 (129) µg/kg lipid; PCB-153, 213 (182) µg/kg lipid; and PCB-180, 209 (158) µg/kg lipid (Domingo *et al.*, 2001). [Although the distribution of congeners differed between the two studies, the PCB concentrations could not be directly compared as the latter values were lipid-adjusted.]

Kitamura *et al.* (2000) reported blood PCB concentrations in Japanese waste workers ($n = 94$) for other PCB congeners: mean (median) PCB-77, 148.59 (149.07) pg/g lipid; PCB-126, 131.81 (98.60) pg/g lipid; and PCB-169, 104.55 (90.45) pg/g lipid. [None of these congeners were measured in the other studies.]

Workers ($n = 15$) employed as operators for incinerators, boiler-maintenance, furnace maintenance, control panel, and waste-gas washing had a mean concentration of total PCBs of 115.7 µg/kg lipid (PCB-28, 0.7 µg/kg lipid; PCB-138, 17.5 µg/kg lipid; PCB-153, 45.5 µg/kg lipid; PCB-180, 52 µg/kg lipid) (Mari *et al.*, 2009). The sum of congeners PCB-138 + PCB-153 + PCB-180 in this study resulted in a total concentration of 115 µg/kg lipid, which was five times lower than that reported in the workers in Spain (573 µg/kg lipid) (Domingo *et al.*, 2001).

In 26 waste-incineration workers from the Republic of Korea, Park *et al.* (2009) found a mean concentration of total PCBs of 214.93 ng/g lipid (median, 161.13 ng/g lipid), of which hexachloro- and heptachloro-congeners accounted for 70% (congeners measured, PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-156, PCB-157, PCB-167, PCB-169, and PCB-189). [Co-exposures to dioxins, furans, and other combustible products found in fly-ash are common for waste-incineration workers.] The waste-incinerator workers did not have statistically significantly higher PCB concentrations than control subjects ($n = 7$) (mean PCB concentration, 19.13 ng/g lipid; median, 94.63 ng/g lipid).

1.5.5 Electronic-waste recycling and scrap-metal dealers

One study reported PCB exposures of workers in e-waste recycling in China (Wen *et al.*, 2008). However, they did not report air or serum PCB concentrations, but PCB concentrations in hair samples collected from 94 workers. The PCB concentration range was 55.4–7200 ng/g.

In 17 scrap-metal dealers in two plants in the USA, mean serum PCB concentrations were 7.5 ppb (range, 1–65.3 ppb) (Malkin, 1995). Serum PCB concentrations were significantly related to eating lunch outside the lunchroom [suggesting hand-to-mouth contact as a source of exposure]. The gas-chromatography peak pattern resembled that of Aroclor 1260. [Both waste recycling and scrap handling result in coexposures to dioxins and metals.]

1.5.6 Locomotive-repair workers

Locomotive-repair workers (n = 120) in the USA were found to have elevated serum concentrations of PCBs, which was attributable to exposure to transformer fluids (Pyranol, Inerteen, Aroclor) (Chase *et al.*, 1982). Workers were divided into three exposure groups: "exposed" workers who had frequent opportunity for direct contact with PCB-containing transformer fluids; "nominally exposed" workers in the facility did not have opportunity for contact with PCBs; and "non-exposed" workers whose work environment did not involve any PCB fluids. Workers' plasma PCB concentrations were: exposed workers, 33.4 ppm (10–312 ppm); nominally exposed workers, 14.2 ppm (10–30 ppm); and non-exposed workers, 12.0 ppm (10–27 ppm).

1.5.7 Miscellaneous use of PCB oil

PCBs can be emitted by several other sources, including light ballasts and microscopic immersion oil, which contains 30–45% PCBs. Fluorescent light ballasts emit PCBs during burnout (IARC, 1978) and air concentrations depend on the distance from the source. Since the previous *IARC Monograph* on PCBs (IARC, 1978), no new studies regarding PCB exposures during work with carbonless copy paper, microscopic immersion oil, or after a fluorescent light ballast burnout have been published.

One study reported a PCB air measurement from a carbonless copy paper stockroom of 0.07 mg/m^3 (Tatsukawa, 1976). Hasegawa *et al.* (1973) reported that blood PCB concentrations in workers in carbonless paper producing plants (0.01–0.02 µg/g) 2 years after exposure were 10% those found during the period when the PCBs were used. No air or biological monitoring data have been published to assess the extent of PCB exposures during the use of microscope oil (Bennett & Albro, 1973). Four and a half hours after burn-out of a ballast, the concentration of PCBs was the highest (166 µg/m^3) 1 m below the burned-out ballast, while the lowest concentration (12 µg/m^3) was found at a distance of 4.5 m from the fixture (Staiff *et al.*, 1974).

In 1958–1978 in Canada, areas around transformers mounted outdoors were treated with phenoxy herbicides (2,4-D and 2,4,5-D) to reduce foliage (Hay & Tarrel, 1997). To increase adherence of the herbicides to the plant leaves, herbicide sprayers (n = 225) would mix 4 pounds [1.8 kg] of phenoxy herbicide with 10 gallons [37.9 L] of used transformer fluid and 90 gallons [340.7 L] of water before spraying. PCB exposures were not measured during this operation.

Use of Aroclor 1254 was reported in a petrochemical plant in the USA during the 1950s, where 31 men had been "heavily exposed" (Bahn *et al.*, 1976). No information regarding how PCB was used was given [but could have been PCBs used as fluids for hydraulic and heat-transfer systems]. No air or blood concentrations of PCBs were reported.

United States navy vessels built between 1946 and 1977 commonly contained PCBs in insulation material, electrical cable, and ventilation

gaskets (Still *et al.*, 2003). In nuclear submarines, PCBs were also used in soundproofing material, missile-launch tubes, electrical cables, banding and sheet rubber, heat-resistant paints, hull coatings, and electrical transformers. Activities associated with PCB exposure during dismantling of these vessels were transformer clean-up and removal; cutting/crushing of PCB-contaminated steel, steel-shot blasting of PCB-contaminated surfaces, chiselling/hand-chipping of PCB-contaminated surfaces, and shoveling/sweeping of PCB-contaminated debris. Surface-wipe sampling showed PCB amounts ranging from non-detects to 11 000 µg/100 cm^2. [Information for PCB exposure in the military is scarce.]

Cumulative lifetime exposure to PCBs among Mohawk men at Akwesasne (a Native American community of more than 10 000 persons located along the St Lawrence River in New York, Ontario, and Quebec) who had been occupationally exposed to PCBs was positively associated with serum total PCB concentration ($P = 0.03$) (other non-occupational sources such as fish consumption and living close to hazardous waste sites discussed in the article are not referenced here). The congener profile was most similar to that of Aroclor 1248, the commercial mixture used at local industrial facilities (Fitzgerald *et al.*, 2007) as a hydraulic fluid in a foundry's die-casting machines from 1959 to 1974, and as a component in aluminium-processing heat-transfer equipment. The occupational exposure of Mohawk men was independently assessed by two occupational hygienists as the probability of exposure to PCBs for all jobs of more than 6 months duration with the following qualitative ratings: (1) definitely not exposed; (2) possibly exposed; (3) probably exposed; and (4) definitely exposed. These ratings were assigned weights of zero, 0.25, 0.5, and 1.0, respectively. The weights for each job were then multiplied by duration of employment in that job, and the results were summed over all jobs to estimate cumulative lifetime occupational exposure to PCBs for each man. [The Working Group noted that this population was also exposed environmentally (see Section 1.4.1(a)).]

A qualitative PCB exposure assessment among welders in Sri Lanka was performed recently (Lankatilake *et al.*, 2012). PCB oil extracted from discarded transformers was widely used as coolant oil in small-scale welding facilities in Sri Lanka to facilitate heat transmission and thereby assist in the cooling process. Exposure to coolant oil occurs during replacement of the coolant and while repairing machinery. The amount of coolant oil used in a welding machine depends on the type of machine, but on average is about 5 L. During repairs, there is a high risk of exposure to PCBs in the transformer oil.

1.5.8 Occupations with exposure to PCB by-products

PCBs have also been reported as a by-product in an electric arc furnace steelmaking plant in the United Kingdom (Aries *et al.*, 2008). Air PCB concentrations in decreasing order by department were: melting shop, 586 pg/m^3 (range, 144–1313 pg/m^3); casting area, 187 pg/m^3 (range, 73–272 pg/m^3); control cabin, 99 pg/m^3 (range, 57–129 pg/m^3). The most prominent congeners were PCB-118 (100–500 pg/m^3), PCB-105 (10–80 pg/m^3), and PCB-77 (5–35 pg/m^3).

Using static high-volume samplers (0.2 m^3/min for 12 hours or 24 hours) in a basic oxygen steelmaking (BOS) and iron ore sintering plant, Jackson *et al.* (2012) calculated mean TEQ pg/m^3 for the by-products PCDD/F and PCBs. The BOS process involves the transfer, desulfurization, and refining of hot metal in a steel converter, and secondary steelmaking treatments. Sintering is a process for blending and fusing iron-ore fines, fluxes, coke, and recycled materials (grit and dusts from other processes). Air concentration ranges were: sinter plant, 0.19–3.72 TEQ pg/m^3 ($n = 12$); and BOS plant, 0.08–0.71 TEQ pg/m^3 ($n = 24$). In

all instances, concentrations of PCBs were much higher than of PCDD/Fs. PCB-126 contributed significantly to the total TEQ (5–20%).

PCBs have been reported as a by-product in penta- and trichlorophenol wood-preservation pesticide manufacturing with PCDFs and PCDDs (Hryhorczuk *et al.*, 1998; Collins *et al.*, 2008). Serum PCB concentrations (sum of PCB-77, PCB-81, PCB-126, and PCB-169) were measured by the company in these workers (Collins *et al.*, 2008): for pentachlorophenol workers only (n = 26; period exposed, 1944–1980) 73.6 pg/g lipid; trichlorophenol workers only (n = 12; period exposed, 1954–1979): 75.9 pg/g lipid; pentachlorophenol and trichlorophenol workers (n = 14; period exposed, 1961–1980): 86.3 pg/g lipid; tradesmen (n = 10): 121.1 pg/g lipid. These PCB concentrations were not much different from those of a selected reference population (n = 36; 75.0 pg/g lipid).

1.5.9 Removal of PCB-containing sealants

PCB-containing sealants were used in building construction before PCBs were banned in that country. For example, sealant used in Sweden contained 4.7–8.1% Clophen A40 (Sundahl *et al.*, 1999). Air PCB concentrations of 10–120 µg/m^3 were reported after removal of the sealant by a variety of methods: cutting the elastic sealant with an oscillating knife; grinding the concrete with a mechanical machine; sawing the concrete with a mechanical saw; or cutting the concrete with a mechanical chisel. The removal methods were changed by equipping the tool with suction, which reduced air PCB concentrations to non-detects to 3.1 µg/m^3 (Kontsas *et al.*, 2004). Serum PCB concentrations in sealant-remover workers were 0.6–17.8 µg/L (mean, 3.9 µg/L; and median, 1.9 µg/L). For highly chlorinated PCBs, the mean was 3.5 µg/L (median, 1.6 µg/L), and for less chlorinated PCBs, the mean was 0.4 µg/L (median, 0.2 µg/L). Correlation between concentrations in air and serum was only noted for PCB-28 and PCB-52.

During sealant removal in Finland, total PCB concentration in dust samples was 0.026 mg/m^3 (Priha *et al.*, 2005). Congeners determined in the sealant were: PCB-28, 82 mg/kg; PCB-52, 3030 mg/kg; PCB-77, 37 mg/kg; PCB-101, 10 325 mg/kg; PCB-118, 6145 mg/kg; PCB-126, 42 mg/kg; PCB-138, 11 765 mg/kg; PCB-153, 11 185 mg/kg; PCB-169, 32 mg/kg; and PCB-180, 7254 mg/kg (Priha *et al.*, 2005).

Swedish construction workers removing PCB-containing sealants had serum PCB concentrations (sum of 19 congeners) of 575 mg/g lipid, while controls (construction workers not involved in PCB abatement work) had levels of 267 mg/g lipid (Seldén *et al.*, 2008; Wingfors *et al.*, 2006). Concentrations of PCB-180 were not significantly different between groups, while concentrations of many less chlorinated PCBs (especially PCB-66 and PCB-56/PCB-60, but also PCB-28, PCB-44, PCB-52, PCB-74, PCB-101, and PCB-105) were much higher in the exposed workers than in the controls.

1.5.10 People working in contaminated buildings

People working in contaminated buildings (office workers, teachers) are exposed to PCBs (Wiesner *et al.*, 2000); PCB concentrations have been surveyed in workers' air (Gabrio *et al.*, 2000; Schwenk *et al.*, 2002; Peper *et al.*, 2005; Schettgen *et al.*, 2012) and blood (Gabrio *et al.*, 2000; Schwenk *et al.*, 2002; Peper *et al.*, 2005; Herrick *et al.*, 2011; Schettgen *et al.*, 2012).

Mean indoor air concentrations of PCBs in three contaminated schools in Germany were reported to be between 77 and 10 125 ng/m^3; 90% of the total PCBs were either PCB-28 or PCB-52 (Gabrio *et al.*, 2000). These congeners were also reported to be found at high concentrations (> 4000 ng/m^3) in other studies in Germany (Schwenk *et al.*, 2002; Peper *et al.*, 2005; Schettgen *et al.*, 2012). The teachers (n = 96) working in the three contaminated buildings had mean

blood PCB-28 concentrations that differed by school (0.045 µg/L, 0.057 µg/L, and 0.098 µg/L, respectively), and that were significantly elevated compared with teachers (n = 55) not working in contaminated schools (range, not detected to 0.035 µg/L) (Gabrio *et al.*, 2000).

Median indoor air concentrations were measured over 2 years in schools in Germany for congeners PCB-28 (33 ng/m³), PCB-52 (293 ng/m³), and PCB-101 (66 ng/m³) (Liebl *et al.*, 2004). Concentrations of more highly chlorinated indicator congeners (PCB-153, PCB-138, and PCB-180) were all below 80 ng/m³. The median sum of indicator congeners was 2.04 µg/m³. Biomonitoring of teachers (n = 9) and cleaning personnel (n = 1) in schools in Germany showed that median blood PCB concentrations exceeded the German reference values after adjusting for age in 8 out of 10 workers for PCB-138, 7 out of 10 for PCB-153, and 8 out of 10 for PCB-180 (Neisel *et al.*, 1999).

In teachers in the USA, the relative contribution of lighter congeners (PCBs 6–74) (mean total serum PCB concentration, 1.86 ng/g; n = 18) was higher than in controls (Herrick *et al.*, 2011). This was also observed in other studies: mean concentration of PCB-28, 0.28 µg/L; PCB-101, 0.07 µg/L; PCB-138, 1.29 µg/L; PCB-153, 1.68 µg/L; and PCB-180, 1.14 µg/L in Peper *et al.*, (2005); median concentration of PCB-28, 0.087 µg/L; PCB-52, 0.024 µg/L; and PCB-101, 0.012 µg/L in Schettgen *et al.*, (2012); and mean concentration of PCB-28, 0.24 µg/L; PCB-52, 0.07 µg/L; PCB-101, 0.02 µg/L; PCB-153, 0.96 µg/L; PCB-138, 0.70 µg/L; and PCB-180, 0.62 µg/L in Schwenk *et al.*, (2002).

People working inside contaminated buildings other than schools may also be exposed to PCBs. In Germany, air PCB concentrations in contaminated commercial buildings were 1280 ng/m³ (PCB-28, 110 ng/m³; PCB-52, 125 ng/m³; PCB-101, 11 ng/m³; PCB-138, < 2 ng/m³; PCB-153, < 2 ng/m³; PCB-180, < 2 ng/m³) (Broding *et al.*, 2007). The PCB contamination originated from insulation material and elastic sealing compounds. Serum PCB concentrations were determined in 2002 for 583 persons who had worked between 1 and 40 years in the contaminated commercial building. The median serum total PCB concentration was 2.32 µg/L (PCB-28, 0.09 µg/L; PCB-52, 0.01 µg/L; PCB-138, 0.55 µg/L; PCB-153, 0.9 µg/L; and PCB-180, 0.7 µg/L). People not working in the contaminated building (n = 205) had significantly lower serum concentrations of PCB-28 and PCB-52 (0.023 µg/L and 0.004 µg/L, respectively) (Broding *et al.*, 2008).

1.5.11 Clean-up of hazardous waste

Occupational exposure to PCBs has also been measured in workers who perform clean-up of hazardous waste. After an explosion and fire of unlabelled chemical waste drums at the former site of Chemical Control Corporation in Elizabeth, New Jersey, USA, the mean air PCB concentration was 0.11 µg/m³ (n = 3) (Costello & King, 1982). In workers (n = 32) removing hazardous waste, including transformers, in the USA, plasma PCB mean concentration was 205 ng/g lipid (range, limit of detection to 527 ng/g lipid) (Horii *et al.*, 2010). Hexa and heptachlorinated biphenyls accounted for 60% of the PCB concentrations.

1.5.12 Firefighters and rescue workers

Firefighters and rescue workers have also been surveyed for PCB exposure in several recent studies, demonstrating a wide variability in serum PCB concentrations (Table 1.33; Kelly *et al.*, 2002; Schecter *et al.*, 2002; Dahlgren *et al.*, 2007; Chernyak *et al.*, 2009, 2012).

1.6 Exposure assessment of epidemiological studies

1.6.1 Studies of occupational exposure

Many epidemiological studies of occupational PCB exposure and cancer have been performed; the majority are among workers in capacitor-manufacture and transformer manufacture and repair. Duration of employment was used to assess exposure in most of these studies (Brown & Jones, 1981; Bertazzi *et al.*, 1982, 1987; Cammarano *et al.*, 1984; Brown, 1987; Nicholson & Selikoff, 1987; De Guire *et al.*, 1988; Taylor *et al.*, 1988; Liss, 1989; Petruska & Engelhard, 1991; Greenland *et al.*, 1994; Tynes *et al.*, 1994; Yassi *et al.*, 1994, 2003; Gustavsson *et al.*, 1986; Savitz & Loomis, 1995; Tironi *et al.*, 1996; Gustavsson & Hogstedt, 1997; Hay & Tarrel, 1997; Kimbrough *et al.*, 1999, 2003; Loomis *et al.*, 1997; Charles *et al.*, 2003; Mallin *et al.*, 2004; Caironi *et al.*, 2005; Prince *et al.*, 2006a, b; Ruder *et al.*, 2006; Ahrens *et al.*, 2007; Hopf *et al.*, 2009b, 2010, 2014; Silver *et al.*, 2009; Pesatori *et al.*, 2013). In the remaining studies, exposure to PCBs was assessed using a variety of approaches, including job-exposure matrices (JEM), development of worker's exposure zones, and measurement of serum PCB concentrations.

JEMs were used in several studies (Greenland *et al.*, 1994; Loomis *et al.*, 1997; Prince *et al.*, 2006a, b; Ruder *et al.*, 2006; Silver *et al.*, 2009).

Greenland *et al.* (1994) developed a JEM in a case–control study of cancer mortality at a transformer-assembly facility. Pyranol was used as the transformer oil from 1936 to 1976. Pyranol was composed of 50% PCBs (mainly hexachlorobiphenyls) and 50% trichlorobenzene, but the PCB content could vary from 45% to 80%. A combination of 1000 job titles in 50 departments in 100 buildings resulted in more than 5500 entries in the JEM. Each entry was rated for seven selected exposures from 1901 to 1984. A four-point categorical rating scale was used to rate the jobs. Former employees and experienced industrial hygienists rated each entry. For pyranol, benzene, and solvents, the analysis categories were: 0, no exposure; 1, indirect exposure, meaning that the chemical was found in the work area, but the worker did not perform tasks using it; 2, direct exposure. Cumulative exposures were calculated using these scores and individual job histories.

A cancer mortality study among electric-utility workers in five companies exposed to PCBs used job categories to estimate weekly exposures in hours for each job (Loomis *et al.*, 1997). PCBs were used in capacitors, transformers and switches. Capacitor fluids were 100% PCBs, while transformer fluids contained 70% PCBs and 30% chlorinated benzene solvents. Exposure assessments were performed by expert panels for each company. The panel members (industrial hygienists, safety personnel, managers, and long-term workers) recorded their individual exposure assessments for PCBs, and other exposures, which were later discussed to resolve differences. For each occupational category and decade, the frequency in times per week and duration in hours of exposure to insulating fluids during the average working week was indicated. This was used to construct company and calendar time-specific JEMs Industrial hygiene surveys of the plants were used to interpret the panel's exposure assessment. Each occupational category (in total, 28) was classified according to workers' potential exposure to PCBs.

Three plant-specific semiquantitative JEMs were used in a study of cancer of the breast in former capacitor-manufacturing workers (women) in Indiana, Massachusetts, and New York, USA (Silver *et al.*, 2009). Two of these JEMs had been used previously in a mortality study (Prince *et al.*, 2006a, b) of former workers at the Indiana and Massachusetts plants, and one in a mortality study of former workers at the Indiana plant (Ruder *et al.*, 2006). Two of the three JEMs have been described in detail in separate publications (Hopf *et al.*, 2009b,

Table 1.33 Serum PCB concentrations in firefighters

Country	Population	Activity	PCB congeners measured	Mean serum PCB concentration	Reference
USA	Firefighters (n = 58)	Extinguishing a transformer fire	NA	2.96 ppb (range, 1.9–9.6 ppb)	Kelly *et al.* (2002)
	Rescue workers (n = 7)	Working during the collapse of the World Trade Center, New York, September 2001	Non-*ortho* PCBs	43–328 pg/g lipid	Dahlgren *et al.* (2007)
			Mono-*ortho* PCBs	19–404 ng/g lipid	
			ΣDL-PCBs[a]	19–405 ng/g lipid	
Russian Federation	Firefighters, symptomatic (n = 8)	Participated in extinguishing a fire at a cable-manufacturing plant (no SCBA)	ΣDL-PCBs[a]	198.6 pg/g lipid	Chernyak *et al.* (2009, 2012), Schecter *et al.* (2002)
	Firefighters, asymptomatic (n = 5)	Participated in extinguishing a fire at a cable-manufacturing plant (no SCBA)	ΣDL-PCBs[a]	198.9 pg/g lipid	
	Firefighters (n = 7)	Other fires	ΣDL-PCBs[a]	231.7 pg/g lipid	
			Congener 77, 126, 169	Symptomatic firefighters > than the other groups	Schecter *et al.* (2002)

[a] DL-PCBs, dioxin-like PCBs, i.e. PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189

NA, not available; PCB, polychlorinated biphenyl; SCBA, self-contained breathing apparatus

2010). Exposure determinants or factors that influenced PCB exposures for each plant were assessed for all jobs listed in the work histories. Jobs with similar rating of the exposure determinants were grouped into exposure categories. Each job-exposure category, exposure intensity (high, medium, low, background) and frequency (continuous, intermittent) were qualitatively rated separately for inhalation and dermal exposure. The plant-specific JEMs used available air PCB concentrations (the same as in Sinks *et al.* (1992) for the Bloomington plant) to assign inhalation weightings. The product of intensity and frequency (fraction of day exposed) was calculated for each job-exposure category. Finally, the JEM was modified for eras with different conditions of PCB exposure (change in Aroclor use, ventilation-system improvements, lay-out changes etc).

[These historical reconstructions are better than using duration of employment alone in the epidemiological studies, since duration does not distinguish between jobs with higher or lower potential for PCB exposure. Most of these retrospective studies involved manufacturing plants that used limited amounts of other chemicals, or at least when other chemicals were used, these jobs were often indicated and could be excluded from the epidemiological analysis. Creating cohorts of today's working environment would include a very diverse industry with multitude of job activities, including an array of different chemicals. Therefore it would be difficult to draw definitive statements on the causations of a possible observed mortality excesses.]

In their retrospective study of mortality, Sinks *et al.* (1992) developed workplace exposure zones to classify worker exposure. The capacitor-manufacturing plant studied was divided into five zones of exposure by drawing consecutive circles (radius, approximately 69 m) centred upon the heaviest source of PCB exposure. The production area was thus divided into three zones by proximity to PCB source. Two other zones were

defined: maintenance and office workers. Air sampling was conducted in these five zones, and means were assigned as the weight (1–5) of PCB exposure for the zone.

Serum PCB concentrations were used in one case–control study (Laden *et al.*, 2001b), and in a recent cross-sectional study (Persky *et al.*, 2012) (see Section 1.5.2).

1.6.2 Studies of environmental exposure

Cohort studies of environmental exposure have used many approaches to assess exposure to PCBs. Exposure approaches include interview, questionnaires, cumulative PCB exposure, dietary intake of fatty fish, PCB concentrations in biological media such as blood, adipose tissue, and breast milk, and in the environment such as carpet dust, or any combinations of these. Biological measures of body burden have been used extensively (see Table 1.34).

1.7 Regulations and guidelines

1.7.1 Global

For Parties to the Stockholm Convention on Persistent Organic Pollutants (POPs) (UNEP, 2001), presently 179 Member States, the production of PCBs is totally prohibited, although the presence of PCBs in equipment is allowed to continue until 2025. The environmentally sound management of waste containing or contaminated with PCBs at a content above 0.005% must be achieved by 2028.

Annex I of the Basel Convention on the Transboundary Movements of Hazardous Wastes and Their Disposal (UNEP, 2011) defines a category of hazardous waste specific to PCBs: "Y10 waste substances and articles containing or contaminated with PCBs and/or polychlorinated terphenyls (PCTs) and/or polybrominated biphenyls (PBBs)." Additionally, Annex VIII defines as "hazardous" any electrical waste containing or contaminated with PCBs at a concentration greater than 50 mg/kg. The Basel Convention is legally binding for 179 countries (status in 2013).

The Codex Alimentarius Commission, recognizing the importance of prevention of human exposure through source-directed measures (i.e. strict control of industrial and agricultural processes that may generate and release PCDDs, PCDFs, and PCBs), adopted the Code of Practice Concerning Source Directed Measures to Reduce Contamination of Food with Chemicals (CAC/RCP 49–2001) (Codex Alimentarius, 2001) and the Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Foods and Feeds (CAC/RCP 62–2006) (Codex Alimentarius, 2006). No limits in foodstuffs were included, but management options were recommended.

(a) Provisional tolerable monthly intake

In 2002, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable intake of 70 pg/kg bw per month for PCDDs, PCDFs, and DL-PCBs expressed as TEFs, based on reproductive end-points (JEFCA, 2002). The value was expressed "per month" to reflect that exposure is cumulative and chronic rather than acute.

(b) Drinking-water

No water quality guidelines have been set for these substances because of their low solubility in water.

(c) Air

Air quality guidelines for PCBs have not been established, because exposure by direct inhalation generally constitutes only a small proportion of total exposure, in the order of 1–2% of the daily intake from food. Although this air concentration is only a minor contributor to direct human exposure, it is a major contributor to contamination of the food-chain (WHO, 2000).

Table 1.34 Common measures of exposure to PCBs and design of the exposure assessment in epidemiological studies in non-occupational settings

Exposure measure	Exposure assessment	Examples of exposure categories reported
Cumulative PCB exposure	Regular jobs held	• Job-exposure schemes • Industry classifications • Potential exposure to PCBs as assessed by an occupational hygienist
Dietary intake of fatty fish containing PCBs	Standardized questionnaires or interviews	• Number of fish meals per day
High-level dietary intake of contaminated rice oil (mass poisoning)	Admission to hospital	• Area of residence
Environmental PCB concentrations	PCB concentrations in carpet dust PCBs in soil	• Amount of PCBs in dust • Amount of PCBs in soil
PCB concentrations in biological samples	Serum PCB concentration, non-lipid adjusted	• Sum of PCB congeners • High or low PCB body burden: 'high' exposure (higher than the median based on the control group) vs. 'low' exposure (lower than the median based on the control group)
	Serum PCB concentration, lipid adjusted	• Sum of PCB congeners measured • Single PCB congeners • Potentially estrogenic PCBs (PCB-44, PCB-54) and PCB-101, PCB-187 • Potentially anti-estrogenic, immunologic, dioxin-like, non-*ortho* substitution, mono-*ortho* substitution, moderately persistent (PCB-66, PCB-77, PCB-105, PCB-118, PCB-126) • Immunotoxic PCBs (PCB-66, PCB-74, PCB-105, PCB-118, PCB-138, PCB-153, PCB-156, PCB-167, PCB-180) • Di-*ortho* substitution, limited DL-PCBs and persistent PCBs (PCB-128, PCB-138, PCB-170) • Biologically persistent inducers of CYP1A and CYP2B • Environmentally relevant PCBs (PCB-195, PCB-206, PCB-209) • Neurotoxic PCBs (PCB-18, PCB-28) • Non-dioxin-like PCBs (PCB-74, PCB-99, PCB-118, PCBs 138–158, PCB-146) • Sum of DL-PCBs (PCB-105, PCB-118, PCB-156) • Sum of NDL-PCBs (PCB-28, PCB-99, PCB-138, PCB-153, PCB-170, PCB-183, PCB-187) • *BRCA1* inhibiting PCBs (PCB-101, PCB-138) • Pseudo-estrogen PCBs (PCB-28, PCB-52, PCB-153) • Phenobarbital inducers (PCB-101, PCB-153, PCB-180, PCB-194) • Most-represented congeners (PCB-118, PCB-138, PCB-153, PCB-180)
	Plasma PCB concentration	Sum of the four most prevalent PCB congeners (PCB-118, PCB-153, PCB-138, PCB-180)
	Adipose tissue PCB concentrations	Sum of 18 PCBs Sum of dioxin-like PCBs (PCB-77, PCB-126, PCB-169)
PCB concentrations in biological samples (cont.)	Tumour tissue PCB concentrations	Sum of PCB congeners (PCB-28, PCB-31, PCB-49, PCB-52, PCB-101, PCB-105, PCB-118, PCB-138, PCB-153, PCB-170, PCB-180), measured at the time of diagnosis

DL-PCB, dioxin-like polychlorinated biphenyl; NDL-PCB, non-dioxin-like polychlorinated biphenyl

1.7.2 Environmental regulations

(a) European Union and Member States

The Member States of the European Union have taken actions to eliminate the production, use, and release of PCBs since 1985. In 2004, to implement the Stockholm Convention on POPs, by regulation EC/850/2004 (EU 850/2004), the production, placing on the market, and use of PCBs were prohibited. Low POPs concentration limits were adopted through Council Regulation (EC) No. 1195/2006 (EU 1195/2006) amending Annex IV to Regulation (EC) No 850/2004. Within the European Union of 26 Member States, several measures have been adopted to reduce the presence of PCDDs, PCDDs, PCDFs, and PCBs in the environment, in food and in feed. These include:

- Commission Regulation (EC) No. 1883/2006 of 19 December 2006 laid down methods of sampling and analysis for the official control of levels of dioxins and DL-PCBs in certain foodstuffs;
- Commission Recommendation 2006/88/EC of 6 February 2006 concerning the reduction of the presence of dioxins, furans and PCBs in feedingstuffs and foodstuffs;
- Commission Recommendation 2006/794/EC of 16 November 2006 on the monitoring of background levels of dioxins, DL-PCBs and NDL-PCBs in foodstuffs.
- The most recent Commission Regulation (EU) No. 1259/2011 amended Regulation EU 1881/2006 as regards maximum levels for DL-PCBs and NDL-PCBs (EC, 2011a); it also changed the formerly used 1998 WHO TEFs to the scheme adopted in 2005 (referred to as WHO_{2005}-TEFs) (Van den Berg *et al.*, 2006) and includes maximum levels for NDL-PCBs in food.

  See Table 1.35

(b) North America

(i) USA

The United States Food and Drug Administration has established tolerance levels in various foods in an attempt to reduce human exposure to PCBs (FDA, 2013). [These limit values were set in 1971 and 1977, before any epidemiological and most experimental studies were conducted, and have not been revised since.] The temporary tolerance levels for PCB residues are as follows:

- 1.5 ppm in milk (fat basis);
- 1.5 ppm in manufactured dairy products (fat basis);
- 3 ppm in poultry (fat basis);
- 0.3 ppm in eggs;
- 0.2 ppm in finished animal feed for food-producing animals (except the following finished animal feeds: feed concentrates, feed supplements, and feed premixes);
- 2 ppm in animal feed components of animal origin, including fishmeal and other by-products of marine origin and in finished animal feed concentrates, supplements, and premixes intended for food-producing animals.
- 2 ppm in fish and shellfish (edible portion). The edible portion of fish excludes head, scales, viscera, and inedible bones;
- 0.2 ppm in infant and junior foods;
- 10 ppm in paper food-packaging material intended for or used with human food, finished animal feed and any components intended for animal feeds. The tolerance does not apply to paper food-packaging material separated from the food therein by a functional barrier that is impermeable to migration of PCB.

The United States Environmental Protection Agency (EPA) has set a maximum contaminant level for PCBs of 0.0005 mg/L (500 ppt) in drinking-water. The EPA requires that spills

Table 1.35 Maximum permitted levels for dioxin-like compounds and indicator PCBs in the European Food and Feed regulation

Foodstuffs	Maximum permitted levels[a]		
	Sum of PCDDs, PCDFs, DL-PCBs[b] (pg WHO_{2005}-TEQ per g fat)	DL-PCBs[b] (pg WHO_{2005}-TEQ per g fat)	Sum of PCB_6[c] (ng/g fat)
Meat and meat products (excluding edible offal) of the following animals):			
Bovine animals and sheep	4.0	1.75	40
Poultry	3.0	0.75	40
Pigs	1.25	0.5	40
Liver of terrestrial animals and derived products thereof	10.0		40
Muscle meat of fish and fishery products and products thereof (with the exemption of wild caught eel and wild-caught fresh water fish, with the exception of *diadromous* fish species caught in fresh water, fish liver and derived products, and marine oils)[a]	6.5 pg/g ww	2.5 pg/g ww	75 ng/g ww
Muscle meat of wild caught fresh water fish, with the exception of *diadromous* fish species caught in fresh water, and products thereof[d]	6.5 pg/g ww		125 ng/g ww
Muscle meat of wild caught eel (*Anguilla anguilla*) and products thereof	10.0 pg/g ww		300 ng/g ww
Fish liver and derived products thereof with the exception of marine oils referred to above	20.0 pg/g ww		200 ng/g ww
Marine oils (fish body oil, fish liver oil and oils of other marine organisms intended for human consumption)	6.0		200
Raw milk and dairy products, including butter fat	5.5	2.0	40
Hen eggs and egg products	5.0	1.75	40
Fat of the following animals:			
Bovine animals and sheep	4.0		40
Poultry	3.0		40
Pigs	1.25		40
Mixed animal fats	2.5	0.75	40
Vegetable oils and fats	1.25		40
Foods for infants and young children	0.2 pg/g ww		1.0 ng/g ww
Fruits, vegetables and cereals		0.1 pg/g ww	

[a] The maximum level expressed on fat is not applicable for foods containing < 2% fat (the maximum level expressed on product basis for foods containing < 2% fat = maximum level expressed on fat for that food × 0.02).

[b] The Commission Recommendation 2011/516/EU (EC, 2011b) replaces regulation 2006/88/EC and sets separate action levels for PCDD/PCDF (expressed as WHO_{2005}-TEQ) and DL-PCB (expressed as WHO_{2005}-TEQ).

[c] PCB_6 comprises PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, and PCB-180

[d] The maximum level for crustaceans applies to muscle meat from appendages and abdomen. In the case of crabs and crab-like crustaceans (*Brachyura* and *Anomura*) it applies to muscle meat from appendages.

DL-PCB, dioxin-like polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; TEQ, toxic equivalent; ww, wet weight

Adapted from EC (2011a) and EC (2011b)

or accidental releases into the environment of 1 pound (0.45 kg) or more of PCBs be reported to the EPA (ATSDR, 1996).

(ii) Canada

The import, manufacture, and sale (for re-use) of PCBs were made illegal in Canada in 1977. Release of PCBs to the environment was made illegal in 1985. However, use of PCB-containing equipment is allowed until the end of its service life. The storage of PCBs has been regulated since 1988. Export has been regulated since 1997. These provisions are maintained in the Chlorobiphenyls Regulations, under the Canadian Environmental Protection Act, 1999 (CEPA, 2011).

The regulation of waste is consistent with the Basel Convention's "Technical guidelines for the environmentally sound management of wastes consisting of, containing, or contaminated with persistent organic pollutants" (Basel Convention, 2007, 2015).

(c) Australia and New Zealand

(i) Australia

The Industrial Chemicals (Notification and Assessment) Act 1989 was amended to give effect to the Stockholm Convention (NICNAS, 1989).

The National Strategy for The Management of Scheduled Waste was endorsed by the Australian and New Zealand Environment and Conservation Council in 2003 (ANZECC, 2003) and provides for the safe management and disposal of organochlorine pesticides, PCBs and hexachlorobenzene. The PCB Management Plan provides treatment provisions for different types of PCB waste including liquid residues and discharges, gaseous emissions, solid residues and disposal (Australian Government, 2006, 2007).

(ii) New Zealand

The Hazardous Substances and New Organisms (HSNO) Act 1996 (as amended by the HSNO [Stockholm Convention] Act Amendment 2003), prohibits the production, use and import of the chemicals listed in Annex A of the Convention, including PCBs. Exempted use of PCBs as per the Toxic Substances Regulations 1983 is permitted, but subject to phase-out no later than December 2016. The HSNO Act 1996 is administered by The New Zealand Environment Risk Management Authority (ERMA) by: assessing new chemicals, pesticides or industrial chemicals currently in use that exhibit POP characteristics (Articles 3.3 and 3.4); permitting the appropriate use of POPs for laboratory-scale research or as a reference standard (Article 3.5); managing the existing exempted use and storage of PCBs (Article 3.6); prohibiting import, manufacture, or use of POPs (Article 3.1 and 3.2). The Imports and Exports (Restrictions) Act 1988, via the Imports and Exports (Restrictions) Prohibition Order (No. 2) 2004, prohibits export of POPs (except as conditionally provided under Article 3.2). Import and export are regulated under The Imports and Exports (Restrictions) Act 1988.

(d) Asia

(i) China

China implements an import and export registration system, included under its Regulations on Environmental Management of Chemicals and the Import and Export of Toxic Chemicals of 1994. In 2005, PCBs were included in the List of Toxic Chemicals Strictly Prohibited from Import and Export, by No. 116 Notice on the List of Goods Prohibited from Import (the Sixth Group). The National Implementation Plan under the Stockholm Convention entered into force for China in 2004, and also applied to the Special Administrative Regions of Hong Kong and Macao (NIP China, 2007). This plan aims to prohibit and prevent the production and import of PCBs, and to achieve the environmentally sound management of currently used equipment containing PCBs. China used to produce PCBs, but production was stopped in the 1970s. The

plan called for establishing a system for the declaration, registration, and environmentally sound management of equipment in use containing PCBs by 2010. Identification of high-risk equipment currently in use across the country is to be achieved by 2015, with uses of PCBs eliminated by 2025.

Furthermore, China has also stipulated special administrative regulations and standards with regard to PCBs. The Notice on the Issues Concerning Prevention of Pollution Caused by Hazardous Polychlorinated Biphenyls was promulgated in 1979 to ban future imports of power equipment containing PCBs. The Notice on Enhancement of the Management over Waste Polychlorinated Biphenyl Power Capacitors was issued in 1990 to forbid trading and dismantling downstream capacitors containing PCBs. The Provisions on the Pollution Caused by Power Installations Containing Polychlorinated Biphenyls and Related Wastes of 1991 addresses the declaration, transfer, transport, import, treatment, disposal, sealing-up and storage of PCB wastes and other sources. The Control Standard on Polychlorinated Biphenyls for Wastes (GB13015–91) was implemented in 1991, in which the value of the control standard on PCBs wastes and the treatment methods for wastes containing PCBs are stipulated (NIP China, 2007).

(ii) Taiwan, China

Importation of PCBs was prohibited in 1980. The Environmental Protection Administration of Taiwan, China, banned the manufacture, sale, and use of PCBs in 1988. An extensive investigation of electrical devices in 1990–1991 indicated that more than 80 000 PCB-containing electrical devices were still in use, mainly capacitors and transformers. A full-scale ban on the use of PCBs, with the exception of experimental, research, and educational purposes, took effect in January 2001. This prohibited use of any electrical devices containing PCBs by the end of 2000, mandating immediate disposal at end of use of capacitors and transformers containing PCBs (Environmental Protection Administration, 1988). Furthermore, PCBs may not be detectable in effluents from business, sewage systems and building sewage-treatment facilities.

(iii) India

According to Schedule VI of the Hazardous Waste (Management, Handling and Transboundary Movement) Rules 2008, the import and export of hazardous wastes, substances and articles containing or consisting of or contaminated with PCBs are prohibited (Ministry of Environment and Forests, 2008).

(e) Africa

United Republic of Tanzania

The Industrial and Consumer Chemicals (Management and Control) Act of 2003 provides for the management and control of PCBs under the list of severely restricted/banned/eliminated chemicals in Schedule 8. The government of the United Republic of Tanzania issued an Environmental Management Act (Government of the United Republic of Tanzania, 2004) that specifically provides for the control and management of current and future POPs, requiring submission of an annual report on implementation.

1.7.3 Occupational exposure limits

(a) USA

The manufacture of PCBs ended in the USA in 1977. Standards for occupational exposures (permissible exposure limits; PELs) in the USA are set by the Occupational Safety and Health Administration (OSHA) (29CFR1910.1000 Table Z-1 Limits for air contaminants). The PELs are 8-hour TWAs unless otherwise noted, and are determined from breathing-zone air samples. The PELs established by OSHA are 1000 μg/m^3 for PCB mixtures containing 42% chlorine, and 500 μg/m^3 for PCB mixtures containing 54%

chlorine (set in 1971 and not revised after this time). Both standards encompass all physical forms of these compounds: aerosols, vapour, mist, sprays, and PCB-laden dust particles. OSHA recognizes that PCBs are absorbed through intact skin; therefore, routes for dermal and inhalation exposure should be evaluated by an industrial hygienist. The National Institute for Occupational Safety and Health (NIOSH) recommends a 10-hour TWA of 1 μg/m^3 based on minimum reliable detectable concentration and the potential carcinogenicity of PCBs. NIOSH also recommends that all workplace exposures be reduced to the lowest feasible level.

(b) Europe

The maximum allowable airborne concentrations for PCBs containing 42% and 54% chlorine in the Federal Republic of Germany [before reunification] were 1.0 and 0.5 mg/m^3, respectively; and in Sweden, 0.5 mg/m^3 (IARC, 1978).

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2. CANCER IN HUMANS

2.1 Cohort studies of occupational exposure

Commercial mixtures of congeners of polychlorinated biphenyls (PCBs) were manufactured starting in the 1920s in Austria, France, Germany, Italy, Japan, Spain, Poland, the Russian Federation, the United Kingdom, and the USA. No published epidemiological studies of cancer among PCB-production workers were available to the Working Group.

2.1.1 Capacitor manufacture

Studies of cancer mortality and incidence among workers exposed to PCBs in the manufacture of capacitors have been conducted in Italy (Bertazzi *et al.*, 1982, 1987; Tironi *et al.*, 1996; Pesatori *et al.*, 2013), Sweden (Gustavsson *et al.*, 1986; Gustavsson & Hogstedt, 1997), and the USA (Brown & Jones, 1981; Brown, 1987; Sinks *et al.*, 1992; Kimbrough *et al.*, 1999, 2003; Mallin *et al.*, 2004; Prince *et al.*, 2006a, b; Ruder *et al.*, 2006; Silver *et al.*, 2009). The details of cohort studies among capacitor-manufacturing workers are presented in Table 2.1.

Bertazzi *et al.* (1982, 1987) studied 544 male and 1556 female former capacitor-production workers exposed between 1946 and 1980 at one capacitor-manufacturing plant in Monza, Italy. Cancer mortality until 1991 was non-statistically significantly increased among men (standardized mortality ratio, SMR, 1.1; 95% CI, 0.7–1.7; 20 deaths) and women (SMR, 1.2; 95% CI, 0.7–1.8; 19 deaths) (Tironi *et al.*, 1996). The most recent update also included 373 male and 97 female workers at a second plant that operated from 1950 to 1982 (Pesatori *et al.*, 2013). There was no excess overall cancer mortality; however, mortality due to cancers of the digestive tract, not otherwise specified, was statistically significantly increased (SMR, 2.5; 95% CI, 1.2–5.3; seven deaths). Deaths due to cancer of the brain (SMR, 1.8; 95% CI, 0.9–3.6; eight deaths) and lymphoma (SMR, 1.9; 95% CI, 1.0–3.3; twelve deaths) were in excess, especially for Hodgkin disease (SMR, 4.0; 95% CI, 1.3–12; three deaths) among women. Men were at increased risk of mortality from cancer of the biliary tract (SMR, 3.9; 95% CI, 1.5–10.4; four deaths) and cancer of the prostate (SMR, 1.7; [95% CI, 0.8–3.5]; seven deaths). [This cohort was notable for the high proportion of women.]

Gustavsson & Hogstedt (1997) studied cancer incidence and mortality until 1991 among 242 male capacitor-manufacturing workers employed for at least 6 months between 1965 and 1978 at a plant in Sweden. Individuals were classified as "high-exposed" if they had ever worked in the impregnation or repair departments. Cancer mortality was not significantly elevated among highly exposed workers (SMR, 1.9; 95% CI, 0.8–3.9; seven deaths). Two cases of cancer of the liver and bile duct were diagnosed (SMR, 6.7; 95% CI, 0.0–37 for highly exposed workers). Mortality from non-Hodgkin lymphoma (NHL) was increased among highly exposed workers based on one case (SMR, 9.1; 95% CI, 0.2–51).

Table 2.1 Cohort studies in capacitor-manufacturing workers

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Tironi *et al.* (1996), Italy, 1954–1982	1556 women, 544 men	Employment, 1 wk, 1946–82	All cancers (140–209)	All women	19	SMR, 1.2 (0.7–1.8)	Update of cohort studied by Bertazzi *et al.* (1982, 1987)
				All men	20	SMR, 1.1 (0.7–1.7)	
			Digestive organs (150–159)	All women	2	SMR, 0.9 (0.1–3.3)	
				All men	10	SMR, 2.0 (0.9–3.6)	
			Lymphatic & haematopoietic (200–209)	All women	5	SMR, 1.4 (0.5–3.3)	
				All men	3	SMR, 2.0 (0.4–5.9)	
			Lymphoma (200–202)	Women	4	SMR, 1.8 (0.5–4.5)	
Pesatori *et al.* (2013), Italy, 1946–1978 (plant 1)	1551 women and 544 men (plant 1); 97 women and 373 men (plant 2)	Employment > 1 wk 1946–1978 (plant 1), all workers employed 1950–1982 (plant 2); PCBs used until 1980	All cancers	All workers	183	SMR, 1.0 (0.9–1.0)	
			Lymphoma (200–202)		12	SMR, 1.9 (1.1–1.3)	
			Digestive NOS (159)		7	SMR, 2.5 (1.2–5.3)	
			Brain		8	SMR, 1.8 (0.9–3.6)	
			Breast	All women	16	SMR, 0.8 (0.5–1.3)	
			Prostate	All men	7	SMR, 1.7 (0.8–3.5)	
Gustavsson & Hogstedt (1997); Gustavsson *et al.* (1986), Sweden, 1965–1991	242 men	Employed > 6 mo, 1965–1978; low, medium, or high exposure to PCBs	All cancers (140–209)	High-exposed	7	SMR, 1.9 (0.8–3.9)	Age, calendar period, country of origin
			Liver (155)	High-exposed	1	SMR, 6.7 (0.02–37)	
			Lung (162)	High-exposed	2	SMR, 2.2 (0.3–8.0)	
			Prostate (185)	High-exposed	1	SMR, 2.2 (0.1–12)	
			Lymphatic & haematopoietic (200–209)	High-exposed	1	SMR, 3.3 (0.1–19)	
			Lymphoma (200–202)	High-exposed	1	SMR, 9.1 (0.2–51)	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Mallin *et al.* (2004), Illinois, USA, 1944–2000	2885 white (25 non-white workers excluded)		All cancers (140–208)	All	347	[SMR, 1.1 (1.0–1.2)]	Sex, age, race, calendar period
			Stomach (151)	All	17	[SMR, 1.9 (1.1–3.1)]	Workers also exposed to trichloroethylene, 1,1,1-trichloroethane, lead solder, mineral oil, lacquer, paint thinner, epoxies, methyl ethyl ketone
			Intestine excluding rectum (152–153)	All	39	[SMR, 1.3 (0.9–1.7)]	
			Biliary passages, liver, & gallbladder (155–156)	All	14	[SMR, 2.4 (1.3–4.1)]	
			Thyroid (193)	Men	3	SMR, 15.2 (3.1–45)	No deaths from thyroid cancer among women
			Rectum (154)	All	7	[SMR, 1.1 (0.5–2.4)]	
			Prostate (185)	Men	9	SMR, 1.1 (0.5–2.0)	
			Breast (174–175)	Men	49	SMR, 1.2 (0.9–1.6)	
			NHL (200, 202)	Women:			No NHL deaths among those who worked 5–9 years. Data not reported for men
				Worked < 1 yr	7	SMR, 2.1 (0.8–4.3)	
				Worked 1–4 yr	4	SMR, 1.6 (0.4–4.1)	
				Worked ≥ 10 yr	2	SMR, 1.9 (0.2–6.8)	
			Oral cavity & pharyn (140–149)	Men only	3	SMR, 1.1 (0.2–3.3)	No deaths among women
Ruder *et al.* (2006), Indiana, USA, 1957–1998	3569	JEM based on department, job, tasks, monitored exposure levels, estimated cumulative exposure for each worker		*Cumulative exposure*			Sex, age, race, calendar period
			All cancers	Lowest tertile (< 11 000 unit-days)	56	SMR, 0.9 (0.7–1.2)	
				Middle tertile (11 000–89 999 unit days)	62	SMR, 0.9 (0.7–1.2)	
				Highest tertile (≥ 90 000 unit-days)	52	SMR, 0.8 (0.6–1.1)	*P* for trend = 0.48
			Melanoma	Lowest tertile	5	SMR, 3.7 (1.2–8.7)	
				Middle tertile	2	SMR, 1.5 (0.2–5.4)	
				Highest tertile	9	SMR, 2.4 (1.1–4.6)	*P* for trend = 0.72
			Brain	Lowest tertile	3	SMR, 1.4 (0.3–4.0)	
				Middle tertile	4	SMR, 1.8 (0.5–4.6)	
				Highest tertile	5	SMR, 2.7 (0.9–6.3)	*P* for trend = 0.016

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Ruder et al. (2006), Indiana, USA, 1957–1998 (cont.)			Breast	Lowest tertile	4	SMR, 1.0 (0.3–2.7)	
				Middle tertile	3	SMR, 0.9 (0.2–2.7)	
				Highest tertile	0	–	
			Prostate	Lowest tertile	1	SMR, 0.5 (0.0–2.7)	
				Middle tertile	2	SMR, 0.8 (0.1–2.7)	
				Highest tertile	1	SMR, 0.3 (0.0–1.8)	
			NHL (200, 202)	Lowest tertile	1	SMR, 0.4 (0.0–2.3)	
				Middle tertile	5	SMR, 1.9 (0.6–4.5)	
				Highest tertile	3	SMR, 1.3 (0.3–3.8)	
			Oral cavity & pharyn	Lowest tertile	2	SMR, 2.0 (0.2–7.1)	
				Middle tertile	0	–	
				Highest tertile	1	SMR, 0.9 (0.0–4.9)	
Prince *et al.* (2006b), Hopf *et al.* (2010), Massachusetts & New York, USA, 1939–1998	14 458	JEM for each plant based on department, job, tasks, monitored exposure levels, estimated cumulative exposure for each worker		Cumulative exposure: referent category < 150 unit-yr			Sex, age, race, calendar period The New York plant was also studied by Kimbrough *et al.* (1999, 2003). Results for 0-yr lag
			All cancers	150 to < 620 unit-yr	229	RR, 1.1 (0.9–1.3)	*P* for trend = 0.03
				620 to < 2300 unit-yr	238	RR, 1.3 (1.1–1.5)	
				≥ 2300 unit-yr	240	RR, 1.3 (1.1–1.5)	
			Melanoma	150 to < 620 unit-yr	2	RR, 0.3 (0.1–1.3)	*P* for trend = 0.83
				≥ 620 unit-yr	6	RR, 0.7 (0.2–1.9)	
			Brain	150 to < 620 unit-yr	5	RR, 0.6 (0.2–1.8)	*P* for trend = 0.32
				620 to < 2300 unit-yr	3	RR, 0.4 (0.1–1.6)	
				≥ 2300 unit-yr	3	RR, 0.5 (0.1–1.7)	
			Stomach	150 to < 620 unit-yr	6	RR, 1.5 (0.5–4.9)	
				620 to < 2300 unit-yr	10	RR, 3.2 (1.1–9.3)	
				≥ 2300 unit-yr	8	RR, 2.9 (0.9–9.2)	*P* for trend = 0.12
			Intestine excluding rectum	150 to < 620 unit-yr	26	RR, 1.5 (0.8–2.6)	*P* for trend = 0.55
				620 to < 2300 unit-yr	26	RR, 1.5 (0.8–2.6)	
				≥ 2300 unit-yr	27	RR, 1.4 (0.8–2.6)	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Prince et al. (2006b), Hopf et al. (2010), Massachusetts & New York, USA, 1939–1998 (cont.)			Rectum	150 to < 620 unit-yr	5	RR, 1.1 (0.3–3.9)	
				620 to < 2300 unit-yr	1	RR, 0.2 (0.0–1.8)	
				≥ 2300 unit-yr	8	RR, 1,4 (0.4–4.3)	*P* for trend = 0.36
			Biliary passages, liver, & gallbladder	150 to < 620 unit-yr	3	RR, 1.7 (0.3–10.0)	
				620 to < 2300 unit-yr	6	RR, 3.1 (0.6–15)	
				≥ 2300 unit-yr	9	RR, 4.2 (0.9–20)	*P* for trend = 0.07
			Breast	150 to < 620 unit-yr	26	RR, 1.1 (0.6–1.9)	
				620 to < 2300 unit-yr	19	RR, 0.8 (0.4–1.4)	
				≥ 2300 unit-yr	27	RR, 1.3 (0.8–2.3)	*P* for trend = 0.26
			Prostate	150 to < 620 unit-yr	5	RR, 1.5 (0.4–5.6)	
				620 to < 2300 unit-yr	7	RR, 2.8 (0.8–9.6)	
				≥ 2300 unit-yr	18	RR, 6.1 (2.0–18)	*P* for trend < 0.01
			NHL (200, 202)	150 to < 620 unit-yr	13	RR, 1.6 (0.7–3.6)	
				620 to < 2300 unit-yr	3	RR, 0.5 (0.1–1.7)	
				≥ 2300 unit-yr	7	RR, 1.2 (0.4–3.3)	*P* for trend = 0.99
			Myeloma (203)	150 to < 620 unit-yr	6	RR, 1.5 (0.5–4.9)	
				620 to < 2300 unit-yr	9	RR, 2.4 (0.8–7.3)	
				≥ 2300 unit-yr	8	RR, 1.9 (0.6–5.9)	*P* for trend = 0.48
Kimbrough *et al.* (2003), New York, USA, 1946–1998	7075	Duration of employment, whether hourly or salaried	All cancers (140–208)	Hourly workers	381	[SMR, 1.0 (0.9–1.2)]	Sex, age, race, calendar period The plant was also studied by Prince *et al.* (2006b) and Silver *et al.* (2009)
				Salaried workers	111	[SMR, 0.8 (0.7–1.0)]	
			Prostate	Hourly workers	17	SMR, 1.3 (0.7–1.8)	
				Salaried workers	4	SMR, 0.5 (0.1–1.4)	
			Brain	Hourly workers	5	[SMR, 0.5 (0.2–1.2)]	
				Salaried workers	6	[SMR, 1.5 (0.6–3.4)]	
			Breast	Hourly workers	32	SMR, 0.9 (0.6–1.3)	
				Salaried workers	6	SMR, 0.9 (0.3–1.9)	
			Skin, including melanoma	Hourly workers	9	[SMR, 1.2 (0.6–2.4)]	
				Salaried workers	6	[SMR, 2.1 (0.8–4.7)]	
			Biliary passages, liver, & gallbladder	Hourly workers	6	[SMR, 0.97 (0.4–2.1)]	
				Salaried workers	1	[SMR, 0.3 (0.0–2.6)]	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Kimbrough et al. (2003), New York, USA, 1946–1998 (cont.)			Intestine excluding rectum	Hourly workers	41	[SMR, 1.3 (0.9–1.7)]	
				Salaried workers	11	[SMR, 0.9 (0.5–1.7)]	
			Rectum	Hourly workers	8	[SMR, 1.2 (0.5–2.4)]	
				Salaried workers	4	[SMR, 1.6 (0.4–4.5)]	
			Oral cavity	Hourly workers	4	[SMR, 2.0 (0.6–5.2)]	
				Salaried workers	1	[SMR, 1.1 (2.9–6.4)]	
Silver *et al.* (2009), Indiana, Massachusetts & New York, USA, 1940–1998	5752 women	JEMs (see Ruder *et al.*, 2006 and Prince *et al.*, 2006b for description) Questionnaire for non-occupational risk factors	Breast	All	257	SIR, 0.8 (0.7–0.9)	Sex, age, race, calendar period. Results for subcohort with questionnaire data (n = 3141). Exposure lagged 10 yr
				Cumulative exposure per 1000 unit-yr:			Age, race, calendar period, ever smoking, parity, age at first live birth, breast cancer in first-degree female relative, age began hormone use
				All women	145	HR, 1.0 (1.0–1.1)	
				White women	131	HR, 1.0 (1.0–1.0)	
				Non-white women	14	HR, 1.3 (1.1–1.6)	

HR, hazard ratio; JEM, job-exposure matrix; mo, month; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; wk, week; yr, year

[Findings based on this small cohort were difficult to interpret because of limited precision.]

A cohort of 2885 white workers employed between 1944 and 1977 at a capacitor-manufacturing facility in Illinois, USA, who were exposed to PCBs (1952–1977), chlorinated naphthalenes (1944–1981), and other chemicals, was followed until 2000 (Mallin *et al.*, 2004). Plant records were incomplete and short-term workers (less than 1 year employment) were least likely (83%) to have been traced. There was excess mortality from cancers of the stomach [SMR, 1.9; 95% CI, 1.1–3.1], liver and biliary tract [SMR, 2.4; 95% CI, 1.3–4.1] and breast [SMR, 1.2; 95% CI, 0.9–1.6]. Women with 5 or more years employment during the period of PCB use had significantly elevated mortality from cancers of the liver and biliary tract (SMR, 5.6; 95% CI, 1.5–14; four deaths) and intestine (SMR, 2.3; 95% CI, 1.0–4.3; nine deaths). Men had excess mortality from cancer of the thyroid (SMR, 15.2; 95% CI, 3.1–45; three deaths), while women had excess mortality from NHL, which was not related to the duration of employment (SMRs, 1.6–2.1). Data on NHL were not reported for men. [Exposure assessment was limited and workers were exposed to multiple chemicals, which hampered attribution of cancer outcomes to PCB exposure.]

The United States National Institute for Occupational Safety and Health (NIOSH) cohort (Ruder *et al.*, 2014) included 25 000 workers at facilities in three states, originally studied separately, in Indiana (Sinks *et al.*, 1992; Ruder *et al.*, 2006) and Massachusetts and New York (Brown & Jones, 1981; Brown, 1987; Prince *et al.*, 2006a, b), and combined for an analysis of cancer of the breast (Silver *et al.*, 2009). Separate job-exposure matrices were developed for each of the plants, based on department, job title, era, company records, information about job tasks, and sampling data (Nilsen *et al.*, 2004; Hopf *et al.*, 2009, 2010), with each worker receiving an estimated cumulative exposure score, so that cancer outcomes could be analysed by level of relative exposure.

Updating vital status until 1998 for the Indiana subcohort (which comprised 3569 workers exposed to PCBs between 1957 and 1977) confirmed the earlier findings of excess melanoma and cancer of the brain (Sinks *et al.*, 1992). Melanoma remained in excess (SMR, 2.4; 95% CI, 1.1–4.6), particularly in the lowest tertile of estimated cumulative exposure (SMR, 3.7; 95% CI, 1.2–8.7; five deaths). Mortality from cancer of the brain (SMR, 1.9; 95% CI, 1.0–3.3) increased with exposure, with a standardized mortality ratio of 2.7 (95% CI, 0.9–6.3; five deaths) in the highest quartile and a significant exposure–response trend in the standardized rate ratio (SRR) ($P = 0.02$). Among those having worked ≥ 90 days, both melanoma (SMR, 2.7; 95% CI, 1.1–5.2) and cancer of the brain (SMR, 2.1; 95% CI, 1.1–3.8) were elevated, especially for women (melanoma: SMR, 6.0; 95% CI, 1.2–17.5; three deaths; cancer of the brain: SMR, 2.9; 95% CI, 0.6–8.4; three deaths). The standardized mortality ratio for mortality from NHL was 1.2 (95% CI, 0.6–2.3) (Ruder *et al.*, 2006).

The original studies in the Massachusetts-New York subcohorts (Brown & Jones, 1981; Brown, 1987) included only 2567 workers considered to be highly exposed to PCBs during 1938–1977 (Massachusetts) or 1946–1977 (New York). The update until 1998 expanded the study population to include 14 458 workers with at least 90 days of potential exposure to PCBs (Prince *et al.*, 2006b). Cancer of the liver, leukaemia and aleukaemia [aplastic anaemia], and NHL were not in excess overall, but mortality from multiple myeloma was (SMR, 1.85; 95% CI, 1.23–2.67). In the New York subcohort, mortality from melanoma was elevated (SMR, 1.79; 95% CI, 0.98–3.0). Mortality from cancer of the stomach was elevated among men (SMR, 1.53; 95% CI, 0.98–2.28) and increased with cumulative exposure (trend, $P = 0.039$). Mortality from cancer of the prostate was not elevated overall (SMR, 1.0; 95% CI, 0.72–1.45),

but increased with cumulative exposure (trend, $P < 0.001$). Mortality from intestinal cancer was elevated among women (SMR, 1.31; 95% CI, 1.02–1.66), especially in categories with higher cumulative exposure, but did not show a clear trend.

[The NIOSH studies were originally reported in multiple, overlapping publications based on several plants, but were subsequently merged into a single cohort. The Working Group regarded the quality of the NIOSH studies as high, and noted that they represented considerable effort to enumerate, expand and update the cohorts and assess exposure using objective job-exposure matrices.]

In addition to the NIOSH studies, separate analyses were conducted independently for the New York plant (Kimbrough *et al.*, 1999, 2003). These studies, which used duration of employment and whether hourly or salaried as surrogates for exposure, reported on virtually the same workers as in the NIOSH New York subcohort (mortality until 1998, employed at least 90 days, 7075 workers versus the 6941 studied by NIOSH), but found no significant excess mortality for any cancers (Kimbrough *et al.*, 1999, 2003). [The Working Group noted that the analyses by Kimbrough included 134 more workers than did Prince et al. but was not able to determine the reason for the discrepancy. In addition, Kimbrough et al. presented results only in subgroups defined by sex and pay grade, limiting the power of the analyses.]

The NIOSH study of cancer of the breast (Silver *et al.*, 2009) included 5752 women employed for at least 1 year in any one of the three capacitor-manufacturing facilities studied previously by NIOSH. Exposure to PCBs was estimated semiquantitatively using job-exposure matrices and information about incident cancer of the breast, parity, age at first live birth, breast cancer in a first-degree female relative, hormone use, and smoking was used in analyses for 3952 women who completed questionnaires. Cancer registries and death certificates up to 1998 were used to identify 281 incident cases. The overall standardized incidence ratio (SIR) for cancer of the breast was 0.8 (95% CI, 0.7–0.9), with little effect of employment duration or cumulative exposure. However, for the 282 women of race identified by questionnaire as "other than white," there was a positive, statistically significant association with cumulative exposure, with a hazard ratio for cancer of the breast of 1.3 (95% CI, 1.1–1.6) per 1000 unit-years of estimated cumulative exposure, while no association was observed in "white" women.

2.1.2 Transformer manufacture and repair

Studies of cancer mortality and incidence among workers exposed to PCBs in the manufacture or repair of transformers have been conducted in Canada (Yassi *et al.*, 1994, 2003), Italy (Caironi *et al.*, 2005), and the USA (Greenland *et al.*, 1994; Table 2.2).

Cancer mortality among a subset of deceased former workers at a transformer-manufacturing plant in Massachusetts, USA, was evaluated for (ever having had) exposure to PCBs (Pyranol) (Greenland *et al.*, 1994). There were positive associations with cancer of the liver and biliary tract (odds ratio, OR, 2.4; 95% CI, 0.6–9.7) and lymphoma (OR, 3.3; 95% CI, 1.1–9.3). In an analysis adjusted for age at death, year of death, and year of hire, the adjusted odds ratio was 2.2 (95% CI, 0.8–6.5) for cancer of the liver and biliary tract and 1.5 (95% CI, 0.55–4.3) for lymphoma. [The Working Group noted that numbers of deaths by site associated with exposure to PCBs were not reported, and job histories were unavailable for 34% of the study population.]

Cancer incidence and mortality until 1995 were studied in a cohort of 2222 men working between 1946 and 1975 at a transformer-manufacturing plant in Manitoba, Canada, where PCBs (Askarels) were used from 1956 to fill large transformers (mineral oils were used in other

Table 2.2 Cohort studies in transformer-manufacturing and transformer-repair workers

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Greenland *et al.* (1994), Massachusetts, USA, 1969–1984	1821 deceased white male workers, aged 21–90 yr, vested in company pension plan	Expert assessment	Oral cavity, larynx, pharynx	Pyranol exposure, ever	NR	OR, 1.1 (0.4–3.4)	Age at death, yr of hire, yr of death. Job history unavailable for 34% of deceased former workers; non-white men and women excluded; workers with > 50% work history unrated for PCBs excluded; deceased < 1969 or not vested (10–15 yr work) excluded. No. of exposed deaths, NR. Pyranol contained about 50% PCB. Other exposures included solvents, machining fluids, asbestos, resins
			Oesophagus		NR	OR, 0.9 (0.2–4.1)	
			Stomach		NR	OR, 0.9 (0.3–3.1)	
			Colon excluding rectum		NR	OR, 0.6 (0.3–1.4)	
			Rectum		NR	OR, 0.9 (0.3–2.3)	
			Pancreas		NR	OR, 1.1 (0.4–2.6)	
			Biliary passages, liver, and gallbladder		NR	OR, 2.4 (0.6–9.7)	
				Pyranol exposure at 97th percentile of control exposure	NR	OR, 2.2 (0.8–6.5)	
			Trachea, bronchus, & lung	Pyranol exposure, ever	NR	OR, 1.0 (0.6–1.6)	
			Prostate		NR	OR, 0.8 (0.4–1.7)	
			Bladder		NR	OR, 0.5 (0.1–2.3)	
			Kidney		NR	OR, 0.4 (0.1–3.4)	
			Lymphoma (200–203)	Pyranol exposure at 97th percentile of control exposure	NR	OR, 3.3 (1.1–9.3)	
					NR	OR, 1.5 (0.6–4.3)	
			Leukaemia (204–208)	Pyranol exposure, ever	NR	OR, 0.5 (0.1–2.1)	
			Brain		NR	OR, 1.1 (0.3–3.9)	

Table 2.2 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Yassi *et al.*(1994, 2003), Manitoba, Canada, 1946–1995; 1950–1995 (mortality); 1969–1995 (cancer incidence)	2222 men			Employment:			
			All cancers	> 1 mo	NR	SMR, 1.2 (1.0–1.5)	13% excluded from original mortality study because of missing identifiers. Total of 261 deaths in cohort until 1995
				> 6 mo	NR	SMR, 1.2 (0.9–1.6)	Total of 104 deaths in subcohort until 1995
				Transformer assembly	NR	SMR, 1.6 (0.9–2.8)	Total of 31 deaths in transformer-assembly department until 1995
			Digestive organs (150–159)	> 1 mo	NR	SMR, 1.3 (0.9–1.9)	
				> 6 mo	NR	SMR, 1.3 (0.6–2.3)	
				Transformer assembly	NR	SMR, 2.7 (1.0–5.9)	
			Stomach	> 1 mo	NR	SMR, 0.8 (0.2–2.3)	
				> 6 mo	NR	SMR, 1.8 (0.4–5.2)	
				Transformer assembly	NR	SMR, 5.1 (9.6–18)	
			Pancreas	> 1 mo	NR	SMR, 3.6 (1.9–6.1)	
				> 6 mo	NR	SMR, 4.8 (2.1–9.5)	
				Transformer assembly	NR	SMR, 7.5 (1.5–2.2)	
			Melanoma	> 6 mo	8	SMR, 1.8 (0.2–6.4)	
			All cancers	> 1 mo	NR	SIR, 1.2 (1.0–1.4)	Total diagnoses, 168
				> 6 mo	NR	SIR, 1.0 (0.8–1.3)	Total diagnoses, 65
				Transformer assembly	NR	SIR, 1.1 (0.6–1.7)	Total diagnoses, 18
			Digestive organs (150–159)	> 1 mo	NR	SIR, 1.4 (1.1–1.9)	
				> 6 mo	NR	SIR, 1.1 (0.6–1.8)	
				Transformer assembly	NR	SIR, 1.6 (0.6–3.4)	
			Stomach	> 1 mo	NR	SIR, 1.3 (0.5–2.7)	
				> 6 mo	NR	SIR, 0.4 (0.0–2.4)	
				Transformer assembly	NR	SIR, 1.7 (0.0–9.5)	

Table 2.2 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Yassi et al.(1994, 2003), (cont.)			Pancreas	> 1 mo	NR	SIR, 2.7 (1.3–4.9)	
				> 6 mo	NR	SIR, 4.3 (1.7–8.8)	
				Transformer assembly	NR	SIR, 7.2 (1.5–21.1)	
			Gall bladder	> 1 mo	NR	SIR, 5.1 (1.4–13)	
				> 6 mo	NR	SIR, 2.9 (0.0–16)	
				Transformer assembly	NR	0	
			Melanoma	> 1 mo	10	SIR, 2.2 (1.1–4.0)	
Caironi *et al.* (2005), Bergamo, Italy, 1950–early 1990s; 1950–2002	471 (372 men, 99 women)		Stomach	All exposed	7	SMR, 1.6 (0.6–2.5)	No. of deaths, but not SMRs reported for other cancers (oral cavity, 4; oesophagus, 1; pancreas, 1; larynx, 2; lung, 18; breast, 3; prostate, 3; bladder, 2; lymphoma, 3; other cancers, 4)
			Intestine excluding rectum (153–4, 159)	All exposed	11	SMR, 2.6 (1.6–3.5)	
			Liver	All exposed	3	SMR, 0.3 (0.0–1.1)	
			Leukaemia (204–208)	All exposed	2	SMR, 1.8 (0.0–3.6)	

HR, hazard ratio; JEM, job-exposure matrix; mo, month; NHL, non-Hodgkin lymphoma; NR, not reported; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio

transformers) (Yassi *et al.*, 2003). The mortality study showed an increased risk of mortality for cancer of the digestive tract, particularly cancers of the stomach and pancreas, among workers in the transformer-assembly department. The incidence study included ten cases of malignant melanoma in the full cohort (SIR, 2.2; 95% CI, 1.1–4.0). Increased risk of cancers of the gall bladder and pancreas was also observed among all workers, and an excess of cancer of the pancreas was reported among workers in the transformer-assembly department (SIR, 7.2; 95% CI, 1.5–21.1) (Yassi *et al.*, 2003). [The Working Group noted that the authors did not assess individual exposure to PCBs, which makes it difficult to attribute effects specifically to PCBs.]

In a study in Bergamo, Italy, among 471 workers who built transformers between 1950 and 1988, using PCBs until 1980 and mineral oils thereafter, and who repaired transformers from 1988 until the early 1990s, mortality from cancer of the intestine was significantly elevated (SMR, 2.6; 95% CI, 1.6–3.5; 11 deaths), but mortality from cancer of the stomach or liver, or leukaemia, was not (Caironi *et al.*, 2005). [This was a small study, but it focused on transformer-repair workers who would have had substantial dermal exposure to PCBs.]

2.1.3 Electric power and telecommunications

Studies of cancer mortality and incidence among workers exposed to PCBs in the electric-power and telecommunications industries have been conducted in Canada (De Guire *et al.*, 1988; Hay & Tarrel, 1997), Italy (Cammarano *et al.*, 1984, 1986), Norway (Tynes *et al.*, 1994), and the USA (Savitz & Loomis, 1995; Loomis *et al.*, 1997; Charles *et al.*, 2003; Table 2.3).

De Guire and coworkers found increased incidence of and mortality from malignant melanoma among 9590 employees of a telecommunications company in Montreal, Canada, who had been employed for 6 months or more between 1976 and 1983 (De Guire *et al.*, 1988, 1992). Three deaths were identified among men (SMR, 3.0; 95% CI, 0.6–8.8), with a stronger association for those with < 20 years latency (SMR, 9.4; 95% CI, 1.1–34; two deaths) than for those with ≥ 20 years latency (one death; SMR, 1.3; 95% CI, 0.0–7.1). Only one case occurred among women (SMR, 4.8; 95% CI, 0.1–27). [This was a reasonably large cohort, but the number of incident cases was small. Exposure to PCBs may have occurred, but was not assessed.]

Cancer incidence among 5088 workers in the hydroelectric-power industry in Norway employed for at least 1 year between 1920 and 1991 was examined in relation to magnetic fields or electric sparks, and to exposure to PCBs (Tynes *et al.*, 1994). Workers were classified as ever or never exposed to PCBs, based on work histories. The incidence of malignant melanoma was increased in the full cohort (SIR, 1.1; 95% CI, 0.7–1.8) and among power-supply electricians (SIR, 2.1; [95% CI, 1.0–3.7]). Significantly increased incidence was also reported among workers ever exposed to PCBs and to > 15 μT-years of magnetic fields (SIR, 2.7; [95% CI, 1.2–5.2]). [This study investigated exposure to PCBs and to electric and magnetic fields. Exposures to PCBs and to electric and magnetic fields may be correlated through associations with certain jobs, but exposure is unlikely to confound the association with PCBs, as such exposure is not known to be associated with melanoma.]

Loomis and colleagues assessed risk of cancer in relation to PCB exposure among 138 905 male employees of five utility companies in California, North Carolina, Pennsylvania, Tennessee, and Virginia, USA, who were employed for at least 6 months between 1950 and 1986 (Savitz & Loomis, 1995; Loomis *et al.*, 1997). Exposures were assessed jointly by representatives of employees and management and by industrial hygienists. Mortality from melanoma increased with increasing exposure to PCBs, from 1.2 (95% CI, 0.6–2.5) for those with < 2000 hours cumulative

Table 2.3 Cohort studies in electric-power and telecommunications workers

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
De Guire *et al.* (1988, 1992), Montreal, Canada, 1976–1983	9590	Working on 1 January 1976 or up to 31 December 1963, ≥ 6 mo employment. Exposed to polyvinyl chloride, soldering fumes, and PCBs	All cancers	Men	67	SMR, 0.6 (0.5–0.7)	
			Oral cavity, larynx, pharynx	Men	1	SMR, 0.2 (0.0–1.0)	
				Women	17	SMR, 0.9 (0.5–1.4)	
			Digestive organs (150–159)	Men	22	SMR, 0.7 (0.4–1-1)	
				Women	5	SMR, 1.2 (0.4–2.9)	
			Trachea, bronchus, lung	Men	26	SMR, 0.6 (0.4–0.8)	
				Women	4	SMR, 1.5 (0.4–4.0)	
			Melanoma	Men	3	SMR, 3.0 (0.6–8.8)	
				Women	1	SMR, 4.8 (0.1–27)	
				Men, < 20 yr latency	2	SMR, 9.4 (1.1–34)	
				Men, ≥ 20 yr latency	1	SMR, 1.3 (0.0–7.1)	
				Women, < 20 yr latency	1	SMR, 12.1 (0.0–67)	
			Eye, brain	Men	2	SMR, 0.5 (0.1–1.7)	
			Lymphatic and haematopoietic (200–208)	Men	7	SMR, 0.7 (0.3–1.5)	
			Bone, breast (170–171, 173–178)	Women	5	SMR, 0.9 (0.3–2.0)	
Tynes *et al.* (1994), Norway, 1920–1991; 1953–1991	5088 men	Worked ≥ 1 yr at any of eight hydroelectric-power companies	Rectum	Employment ≥ 1 yr	27	SIR, 1.1 (0.7–1.6)	
			Lung		68	SIR, 1.1 (0.9–1.4)	
			Breast		1	SIR, 1.1 (0.0–76)	
			Prostate		90	SIR, 1.1 (0.9–1.3)	
			Bladder		27	SIR, 0.8 (0.5–1.2)	
			Melanoma		19	SIR, 1.1 (0.7–1.8)	
			Brain		13	SIR, 0.9 (0.5–1.5)	
			Lymphoma		12	SIR, 0.7 (0.4–1.2)	
			Leukaemia		11	SIR, 0.9 (0.5–1.6)	
			Melanoma	Ever exposed to PCBs	9	SIR, 1.8 [0.8–3.4]	Incidence of other cancers not analysed in association with PCB exposure
				Ever exposed to PCBs, 0–15 μT-yr	0		
				Ever exposed to PCBs, > 15 μT-yr	9	SIR, 2.7 [1.2–5.2]	

Table 2.3 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Loomis *et al.* (1997), California, North Carolina, Pennsylvania, Tennessee, Virginia, USA, 1950–1988	138 905 men	Employed > 6 mo, 1950–1986, exposures assessed by panels of workers, hygienists, managers; calculated cumulative exposure to insulating fluids containing PCBs	All cancers	Potential PCB exposure:			Age, calendar time, race, social class, active work status.
				> 0 to < 5 year	916	RR, 2.2 (0.9–1.2)	
				5 to < 10 year	454	RR, 1.0 (0.9–1.2)	
				10 to < 20 year	601	RR, 1.1 (1.0–1.2)	
				≥ 20 year	656	RR, 1.1 (1.0–1.2)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0–2000	2605	RR, 1.0 (1.0–1.1)	
				> 2000–10 000	331	RR, 1.2 (1.1–1.3)	
				> 10 000	81	RR, 1.0 (0.8–1.3)	
			Brain	Potential PCB exposure:			Age, calendar time, race, social class, active work status, magnetic fields, solvents
				0 to < 5 yr	32	RR, 1.3 (0.8–2.2)	
				5 to < 10 yr	15	RR, 1.4 (0.7–2.6)	
				10 to < 20 yr	17	RR, 1.3 (0.7–2.4)	
				≥ 20 yr	12	RR, 1.1 (0.6–2.2)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0–2000	66	RR, 1.0 (0.7–1.6)	
				> 2000–10 000	5	RR, 0.7 (0.3–1.9)	
				> 10 000	0	RR, 0.0 (0.0–2.6)	
			Liver (155)	Potential PCB exposure:			Age, calendar time, race, social class, active work status, solvents
				0 to < 5 yr	13	RR, 1.1 (0.5–2.3)	
				5 to < 10 yr	5	RR, 0.8 (0.3–2.2)	
				10 to < 20 yr	13	RR, 1.8 (0.9–3.6)	
				≥ 20 yr	5	RR, 0.7 (0.3–1.9)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0 to 2000	29	RR, 0.5 (0.3–0.5)	
				> 2000–10 000	3	RR, 0.4 (0.1–1.4)	
				> 10 000	1	RR, 0.4 (0.1–3.0)	

Table 2.3 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Loomis et al. (1997), (cont.)			Melanoma	Potential PCB exposure:			Age, calendar time, race, social class, active work status, occupational sunlight, wood preservatives
				0 to < 5 yr	25	RR, 1.3 (0.6–2.6)	
				5 to < 10 yr	9	RR, 1.1 (0.5–2.7)	
				10 to < 20 yr	11	RR, 1.4 (0.6–3.3)	
				≥ 20 yr	8	RR, 1.6 (0.6–4.2)	
				Cumulative PCB exposure (h), 0-yr lag:			
				> 0–2000	73	RR, 1.2 (0.6–2.5)	
				> 2000–10 000	12	RR, 1.7 (0.7–7.1)	
				> 10 000	3	RR, 1.9 (0.5–7.1)	
				Cumulative PCB exposure (h), 20-yr lag:			
				> 0 to 2000	42	RR, 1.3 (0.8–2.2)	
				> 2000–10 000	8	RR, 2.6 (1.1–6.0)	
				> 10 000	1	RR, 4.8 (1.5–15)	
				RR per 2000 h cumulative PCB exposure (continuous variable):			
				0-yr lag	-	RR, 1.02 (0.99–1.05)	
				20-yr lag	-	RR, 1.05 (1.01–1.09)	
Charles *et al.* (2003), California, North Carolina, Pennsylvania, Tennessee, Virginia, USA, 1950–1988	387 cases of prostate cancer and 1935 controls matched on age at risk	See Loomis *et al.* (1997)	Prostate (185)	Cumulative PCB exposure (h):			Age-matched and adjusted for race Same cohort studied by Loomis *et al.* (1997)
				< 1.9	94	OR, 1.0	
				1.9 to < 12.6	85	OR, 0.9 (0.6–1.2)	
				12.6 to < 620.1	105	OR, 1.1 (0.8–1.5)	
				620.1 to < 2821.4	55	OR, 0.8 (0.6–1.2)	
				≥ 2821.4	48	OR, 1.2 (0.8–1.7)	

Table 2.3 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Charles et al. (2003) (cont.)				Cumulative PCB exposure (h), 5-yr lag:			
				< 1.6	91	OR, 1.0	
				1.6 to < 12.1	87	OR, 0.9 (0.6–1.2)	
				12.1 to < 597.9	104	OR, 1.1 (0.8–1.5)	
				597.9 to < 2763.2	58	OR, 0.9 (0.6–1.3)	
				≥ 2763.2	47	OR, 1.1 (0.8–1.7)	
				Cumulative PCB exposure ≥ 2763.2 h and EMF ≥ 4.4 μT-yr	35	OR, 1.5 (1.0–2.2)	Equivalent results for total cumulative exposure
Hay & Tarrel (1997), New Brunswick, Canada, 1950–1966; 1950–1992	225 men		All cancers	First sprayed 1950–1958	18	SMR, 1.5 (0.9–2.3)	Sprayed vegetation under power lines with 2,4-D and 2,4,5-T; 1958–66, waste transformer oil with PCBs added to herbicides
				First sprayed 1959–1966	3	SMR, 1.1 (0.2–3.2)	
Cammarano *et al.* (1984, 1986), Milano, Italy, 1960–1969; 1969–1985	270 men	Working on 1 January 1960 or up to 31 December 1969, ≥ 6 mo employment		Exposure:			Exposed to PAHs, asbestos, hydrazine, chromium, nickel, beryllium, and PCBs SMRs from Cammarano *et al.* (1986) All other cancer sites had one or zero death
			All cancers	≥ 10 yr	18	[SMR, 2.2 (1.3–3.4)]	
			Stomach	≥ 10 yr	3	[SMR, 3.0 (0.6–8.7)]	
			Trachea, bronchus, lung	≥ 10 yr	5	[SMR, 1.8 (0.6–4.1)]	
			Bladder	≥ 10 yr	2	[SMR, 7.4 (0.9–26)]	

EMF, electromagnetic fields; mo, month; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; wk, week; yr, year

exposure to PCBs, to 1.7 (95% CI, 0.7–7.1) among those with 2000–10 000 hours cumulative exposure, to 1.9 (95% CI, 0.5–7.1) for those with > 10 000 hours of cumulative exposure over their career. When exposure was lagged by 20 years, the respective relative risks were 1.3 (95% CI, 0.8–2.2), 2.6 (95% CI, 1.1–6.0), and 4.8 (95% CI, 1.5–15.0). When the risk of melanoma was modelled with a continuous variable for cumulative exposure to PCBs, the relative risk per 2000 hours of exposure was 1.05 (95% CI, 1.01–1.09) with a 20-year lag. There was no association with cancer of the liver, and the association with cancer of the brain was less strong: the relative risk was 1.6 (95% CI, 0.9–3.0) among those with < 2000 hours cumulative exposure and 1.8 (95% CI, 0.8–4.0) among those with 2000–10 000 hours cumulative exposure, but there were no deaths from cancer of the brain among those with > 10 000 hours cumulative exposure (Loomis *et al.*, 1997).

A nested case–control study within this utility-worker cohort investigated mortality from cancer of the prostate relative to exposure to electromagnetic fields and PCBs (Charles *et al.*, 2003). Cases were 387 prostate-cancer decedents; 1935 controls (5 per case) were randomly selected from the risk sets of the cases. The odds ratio for cumulative exposure to PCBs for ≥ 2821.4 hours and mortality from cancer of the prostate, adjusted for age and race, was 1.2 (95% CI, 0.8–1.7). For workers with ≥ 2763.2 hours of exposure to PCBs and ≥ 4.4 μT years of exposure to magnetic fields, the adjusted odds ratio was 1.5 (95% CI, 1.0–2.2).

[The Working Group considered that, because of the size of the cohort and the efforts to assess exposure, the Loomis–Charles studies were the strongest in this group, especially the results showing an exposure–response effect. The lagged analysis of melanoma mortality was informative about exposure-time windows.]

Some information about cancer risk among electrical workers with exposure to PCBs was reported in two smaller studies. Hay & Tarrel (1997) investigated mortality in 1958–1991 among power-company workers in Canada who applied mixtures of the pesticides 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and waste transformer oil that contained up to 10% PCBs. All-cancer mortality was increased among workers who first sprayed in 1958 or earlier (SMR, 1.5; 95% CI, 0.9–2.3; 18 deaths), but not among those first exposed in 1959 or later, when used transformer oil was added to the pesticide mix (SMR, 1.1; 95% CI, 0.2–3.2; three deaths). [The Working Group noted that the results were not presented by cancer site and concluded that exposures to PCBs were likely to have been negligible.]

Mortality until 1985 was investigated among 270 men who had worked for at least 6 months in a thermoelectric power plant in Italy and who were exposed to PCBs, chromium, nickel, beryllium, polycyclic aromatic hydrocarbons (PAHs), asbestos, and hydrazine (Cammarano *et al.*, 1984, 1986). Among workers with > 10 years exposure, 18 cancer deaths occurred [SMR, 2.2; 95% CI, 1.3–3.4] (Cammarano *et al.*, 1986). [The Working Group noted that workers were exposed to several human carcinogens and that the study was very small, with only one death for most cancer sites, making it difficult to interpret site-specific mortality.]

2.1.4 Miscellaneous industries

As PCBs have been used in many applications, workers in many industries have been exposed, and as structures and equipment that contain PCBs are repaired, demolished, or replaced, workers involved in these operations and/or in waste recycling and disposal may be exposed. There have been many reports of PCB exposure levels and existing or potential health effects associated with exposure to materials containing PCBs, but studies of cancer are very limited.

Robinson *et al.* (1999) conducted a proportionate mortality study of 31 068 deceased,

unionized, electrical workers employed in the construction industry, who might have been exposed to PCBs (and other agents) during their working lives. Excess mortality occurred for melanoma (proportionate mortality ratio, PMR, 1.23; 95% CI, 1.02–1.47) and cancer of the prostate (PMR, 1.07; 95% CI, 1.00–1.14). [Although this very large death-certificate study found an excess risk for cancers that have been associated with exposure to PCBs in other PCB-exposed cohorts, exposure in this cohort could not be confirmed.]

Unspecified industrial uses of PCBs have been associated with an increased risk of cancer. Bahn and colleagues reported two cases of malignant melanoma among 31 workers in research and development and refinery industries in New Jersey, USA, who were exposed to PCB mixtures, where 0.04 cases would be expected [SIR, 50.0; 95% CI, 5.6–217] (Bahn *et al.*, 1976).

2.2 Cohort studies of environmental exposure

2.2.1 Accidental exposure to PCBs

(a) Cancer mortality in Yusho patients, Japan

The first evaluation by IARC of the possible carcinogenic risk of human exposure to PCBs reported the accidental exposure to PCBs through ingestion of rice oil contaminated by Kanechlor 400 in 1968 in western Japan (see Section 1). In an early analysis of deaths occurring up to 5.5 years after exposure among 1200 Yusho patients, nine deaths from malignant neoplasms were reported, including three tumours of the stomach, two tumours of the lung, one cancer of the liver, one of the breast, and two lymphomas (Urabe, 1974; Kuratsune, 1976). A first update considered mortality among 1761 Yusho patients followed up until 1983 (Kuratsune *et al.*, 1988). Among men, there was a statistically significant increase in mortality from all neoplasms (SMR, 2.13; 95% CI, 1.5–3.0), and particularly cancer of the liver (SMR, 5.6; 95% CI, 2.6–10.7), and lung (SMR, 3.2; 95% CI, 1.4–6.3). No statistically significant increase in tumours was reported among the women.

After these early reports, two other mortality analyses of this cohort have been published with follow-up periods up to 1990 and up to 2007 respectively (see Table 2.4). The first report (Ikeda & Yoshimura, 1996) analysed the mortality of 1815 patients (916 men and 899 women), with an average follow-up of 17 years. In the 40-year follow-up of the total of 1918 patients registered as of 31 December 2007 (Onozuka *et al.*, 2009), 254 cases who had not been diagnosed as Yusho from the beginning of the incident were excluded, leaving 1664 cases for analysis (860 men and 804 women). Of the 269 deaths among men, there was a significant excess mortality from all cancers (SMR, 1.37; 95% CI, 1.11–1.66), and from cancers of the lung (SMR, 1.75; 95% CI, 1.14–2.57) and liver (SMR, 1.82; 95% CI, 1.06–2.91). For women, mortality for cancer of the liver was in excess, although not significantly so (SMR, 1.95; 95% CI, 0.78–4.01). Analysis of different periods since the incident showed that the increased risk for all malignancies, and for cancers of the lung and liver tended to decrease over time.

A more recent analysis that did not exclude the 254 patients diagnosed after 1977 (Yoshimura, 2012) reported essentially the same pattern of mortality, with slightly weaker standardized mortality ratios for cancers of the lung and liver (Table 2.4).

Finally, another analysis of mortality of Yusho patients followed up until 2007 was restricted to the area of Tamamoura in the Goto Archipelago (Nagasaki prefecture), because it was the most severely affected (Kashima *et al.*, 2011). Standardized mortality ratios for all cancers, lung cancer, and liver cancer were estimated using the rates of Nagasaki prefecture as the reference and compared for the years 1968–77 and 1978–2002. A slight excess cancer of the

Table 2.4 Cohort studies of cancer associated with poisoning from rice oil contaminated with PCBs in Japan and Taiwan, China

Reference, location follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases/ deaths	SMR (95% CI)	Covariates Comments
Yusho patients							
Onozuka *et al.* (2009) Fukuoka and Nagasaki, Japan 1968–2007	1664 Yusho patients	Mass poisoning by contaminated rice oil		Overall, compared with national death rates	100 men, 33 women		Age, sex Total number of Yusho patients was 1918, but 254 subjects registered after 1977 (not diagnosed as Yusho from the beginning of the incident) were excluded in this analysis
		Men	All cancers		100	1.37 (1.11–1.66)	
			Liver		17	1.82 (1.06–2.91)	
			Lung		26	1.75 (1.14–2.57)	
			Stomach		20	1.17 (0.72–1.81)	
			Rectum		2	0.65 (0.08–2.36)	
			Pancreas		6	1.49 (0.55–3.24)	
			Leukaemia		2	1.19 (0.14–4.29)	
		Women	All cancers		33	0.75 (0.51–1.05)	
			Liver		7	1.95 (0.78–4.01)	
			Lung		4	0.82 (0.22–2.11)	
			Stomach		2	0.22 (0.03–0.81)	
			Rectum		1	0.56 (0.01–3.10)	
			Pancreas		3	1.02 (0.21–2.98)	
			Leukaemia (204–206)		0	0.00 (0.00–3.25)	
			Breast		3	0.93 (0.19–2.72)	
			Uterus		3	1.14 (0.24–3.33)	
Yoshimura (2012) Fukuoka and Nagasaki, Japan 1968–2007	1918 Yusho patients	Mass poisoning by contaminated rice oil		Overall, compared with national death rates			Age, sex As for Onozuka *et al.* (2009), including the 254 subjects registered after 1977
		Men	All cancers		106	1.26 (1.03–1.53)	
			Liver		18	1.67 (0.99–2.63)	
			Lung		27	1.56 (1.03–2.27)	
			Stomach		21	1.09 (0.68–1.67)	
		Women	All cancers		46	0.89 (0.65–1.17)	
			Liver		8	1.87 (0.81–3.69)	
			Lung		5	0.86 (0.28–2.01)	
			Stomach		4	0.39 (0.11–0.99)	

Table 2.4 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases/ deaths	SMR (95% CI)	Covariates Comments
Kashima *et al.* (2011) Fukuoka and Nagasaki, Japan 1968–2002	533 Yusho patients from Tamamoura area	Mass poisoning by contaminated rice oil		Rates from Tamamoura, compared with Nagasaki prefecture	329 (total)		Age, sex As for Onozuka *et al.* (2009) for both sexes combined, using different reference population; Tamanoura was the most affected area Liver cancer was not mentioned in the analysis of the period 1968–77
		1968–77	All cancers		86	1.13 (0.92–1.40)	
			Lung		11	1.37 (0.76–2.48)	
		1978–2002	All cancers		243	1.03 (0.91–1.17)	
			Liver		21	0.77 (0.50–1.18)	
			Lung		37	0.87 (0.63–1.20)	
Yucheng patients							
Tsai *et al.* (2007) Three counties in central Taiwan, China 1980–2003	1823 Yucheng patients	Mass poisoning by contaminated rice oil		Overall, compared with national death rates	215 deaths (129 men, 86 women)		Age, sex There was also a significant association for mortality by chronic liver disease and cirrhosis (ICD-9 571)
		Men (n = 841)	All cancers		29	0.9 (0.6–1.3)	
			Nasopharynx		3	2.3 (0.5–6.8)	
			Liver & intrahepatic bile ducts		4	0.5 (0.1–1.2)	
			Lung		7	1.1 (0.4–2.2)	
			Lymphatic & haematopoietic (200–208)		4	2.3 (0.6–6.0)	
		Women (n = 987)	All cancers		12	0.7 (0.3–1.1)	
			Nasopharynx		0	–	
			Liver & intrahepatic bile ducts		4	1.6 (0.4–4.1)	
			Lung		1	0.3 (0.0–1.9)	
			Lymphatic & haematopoietic		0	–	
		Both sexes	All cancers		41	0.8 (0.6–1.1)	
			Nasopharynx		3	1.6 (0.3–4.7)	
			Liver & intrahepatic bile ducts		8	0.7 (0.3–1.4)	
			Lung		8	0.8 (0.4–1.6)	
			Lymphatic & haematopoietic (200–208)		4	1.3 (0.4–3.4)	

Table 2.4 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases/ deaths	SMR (95% CI)	Covariates Comments
Li *et al.* (2013) Three counties in central Taiwan, China 1980–2008	1803 Yucheng patients and 5170 referents (neighbours)	Mass poisoning by contaminated rice oil		Overall, compared with neighbourhood referents	295 deaths (178 men, 117 women)		Age, sex, community Significant association for mortality from chronic liver disease and cirrhosis (ICD-9 571)
		Men (n = 830)	All neoplasms (148–239)		46	1.3 (0.9–1.7)	
			Liver & intrahepatic bile ducts (155)		4	0.4 (0.1–1.1)	
			Trachea, bronchus & lung (162)		10	1.5 (0.8–2.7)	
			Stomach (151)		7	3.5 (1.5–7.0)	
			Lymphatic & haematopoietic (200–208)		5	3.0 (1.1–6.6)	
			Thyroid gland (193)		0	–	
		Women (n = 973)	All neoplasms (148–239)		21	0.8 (0.5–1.2)	
			Liver & intrahepatic bile ducts (155)		6	2.1 (0.9–4.5)	
			Trachea, bronchus & lung (162)		1	0.4 (0.0–1.7)	
			Stomach (151)		1	0.5 (0.0–2.5)	
			Lymphatic & haematopoietic (200–208)		0	–	
			Thyroid gland (193)		2	2.0 (0.3–6.7)	
			Breast, female (174)		4	1.1 (0.4–2.7)	
		Both sexes	All neoplasms (148–239)		67	1.1 (0.8–1.4)	
			Liver & intrahepatic bile ducts (155)		10	0.9 (0.4–1.5)	
			Trachea, bronchus & lung (162)		11	1.1 (0.6–1.9)	
			Stomach (151)		8	2.0 (0.9–3.8)	
			Lymphatic & haematopoietic (200–208)		5	1.5 (0.6–3.4)	
			Thyroid gland (193)		2	2.2 (0.4–7.2)	

PCB, polychlorinated biphenyl; SMR, standardized mortality ratio

lung was observed in Tamamoura in 1968–77 (SMR, 1.37; 95% CI, 0.76–2.48) [data for cancer of the liver not reported for that period] and no increase in mortality was seen during the later period (Table 2.4). However, significant excess mortality for all cancers, and for cancers of the lung or liver, were observed for the rest of the Goto Archipelago (excluding Tamamoura) in 1978–2002.

[The Working Group noted that excess cancer mortality was largely restricted to men. In addition the excesses of cancers of the lung and liver were observed in the full population of Yusho patients in analyses using national references rates, but not in the subset from the Tamamoura area analysed using local reference rates. Important confounders such as tobacco smoking for cancer of the lung, or viral hepatitis for cancer of the liver could not be taken into account directly, although they may have been partially controlled for by using local reference rates, if the distribution of such confounders in the local reference population were similar to that of the study population. Yusho patients were also exposed to PCDFs. The possibility of confounding by other exposures therefore could not be completely ruled out.]

(b) Cancer mortality in Yucheng patients, Taiwan, China

In 1979, about 10 years after the incident in western Japan, a similar food poisoning incident occurred in three counties (Taichung, Changhua, and Miaoli) of central Taiwan, China (see Section 1). About 2000 residents from these counties had ingested rice oil contaminated with PCBs, and showed clinical manifestations similar to those described for Yusho (skin eruptions and pigmentation, ocular hypersecretion, and peripheral neuropathy); the syndrome was named 'Yucheng' ('oil disease' in Chinese) (see Section 4). Two mortality analyses have been carried out on this exposed cohort, after 12 and 24 years of follow-up, and are summarized in Table 2.4. The first study cohort was based upon 2038 cases registered until 1979; after excluding 99 cases for which vital status could not be assessed, 1940 [sic] Yucheng patients (929 men, 1011 women) remained for analysis of mortality (Hsieh *et al.*, 1996). During 1980–91, 11 deaths from malignancies were observed (8 men, 3 women); overall and sex-specific mortality was non-significantly lower than among the general population, using either local or national reference rates. Data for specific tumour sites were sparse, and included one death from Hodgkin lymphoma and two deaths from cancer of the liver (one man and one woman). Another analysis of the same study population was conducted with the same follow-up (1980–91), but further exclusions, leaving 1837 patients for analysis and 10 observed deaths from cancer (Yu *et al.*, 1997). Although the standardized mortality ratio for all cancers differed substantially from that in the previous analysis, it was not significantly different from that expected based on national rates (SMR, 1.2; 95% CI, 0.6–2.3). Data for specific cancer sites were not reported. [The Working Group noticed the discrepancy between estimates of standardized mortality ratio based upon apparently very similar data sets.]

Data for updated analyses of Yucheng patients are shown in Table 2.4. Tsai *et al.* (2007) extended the follow-up to 2003. From a list of 2061 registered patients, 70 exposed in utero and 168 who could not be traced were excluded, leaving 1823 patients. Forty-one deaths by cancer were observed between 1980 and 2003. Mortality from all neoplasms was not statistically different from that in the population in Taiwan, China, overall or by sex; mortality from cancers at several sites, including liver, lung, and the lymphatic and haematopoietic system, was also similar to that of the national population. As in a previous study, mortality from chronic liver disease and cirrhosis was significantly increased. [The Working Group noted that chronic liver disease and cirrhosis are important risk factors for cancer of the liver,

together with infection with hepatitis B and C viruses, and tobacco smoking.]

A second updated analysis of Yucheng patients extended the follow-up to 2008 (Li *et al.*, 2013). As referents for comparison, the authors used subjects from the registry set up in 1979, residents of the same community, of the same sex and age (within 3 years) as the Yucheng patients, but who did not meet the criteria to be considered as Yucheng patients. After exclusions because of missing or inconsistent data, a total of 1803 Yucheng subjects and 5170 neighbourhood referents were considered for analysis; a total of 67 Yucheng patients died from cancer during 1980–2008. No significant association with all cancer mortality was found overall or among women. Among men, increased mortality was reported for cancer of the stomach (SMR, 3.5; 95% CI, 1.5–7.0, seven deaths) and neoplasms of lymphatic and haematopoietic tissue (SMR, 3.0; 95% CI, 1.1–6.6, five deaths). Mortality from cancer of the liver was elevated among women (SMR, 2.1; 95% CI, 0.9–4.5, six deaths), but not among men (SMR, 0.4; 95% CI, 0.1–1.1, four deaths). [The neighbourhood referent population used in this study may also have been exposed, which would lead to underestimation of relative risks.]

[The Working Group noted that the excess mortality from all cancers and tumours of the liver observed in Yusho patients was not present in Yucheng patients. The composition of PCDF isomers differed markedly between the two incidents: the main PCDF isomer in Yusho patients was 2,3,4,7,8-pentachlorinated dibenzofuran, which has a higher toxic equivalency factor than the main isomer affecting Yucheng patients, 1,2,3,4,7,8-hexachlorinated dibenzofuran (Onozuka *et al.*, 2009). On the other hand, no excess mortality for cancers of the stomach or lymphatic and haematopoietic tissue was observed in the Yusho patients. The same other limitations mentioned for the Yusho cohort applied to the Yucheng studies: residual confounding, or chance due to multiple comparison made in these analyses could not be discounted.]

2.2.2 Dietary exposure to PCBs

See Table 2.5

Apart from incidental contamination, chronic exposure to PCBs may occur through a diet rich in foods with a high content of PCBs; such exposure has been observed in northern Europe in populations with a high consumption of fish.

Cohorts of fishermen from the east coast and west coasts of Sweden were established in 1968 and 1965 respectively (Rylander & Hagmar, 1995; Svensson *et al.*, 1995). Women who were, or had been, married to these fishermen were identified from national and local population registries. After exclusion because of death, divorce, or emigration, the respective cohorts of fishermen's wives included 1986 women on the east coast and 6605 women on the west coast (Rylander & Hagmar, 1995). Information on vital status and cancer incidence up to 1989 was gathered from Swedish statistics and the Swedish cancer registry. Cancer incidence was compared directly between the cohorts on the east coast (contaminated) and west coast (control), with adjustment for age and calendar year. The incidence rate ratio (IRR) for all cancers was 1.19 (95% CI, 1.00–1.41). Among specific cancer sites, risk was increased for cancer of the breast (IRR, 1.35; 95% CI, 0.98–1.86), cervix (IRR, 1.93; 95% CI, 0.83–4.50) and corpus uteri (IRR, 1.16; 95% CI, 0.61–2.20). All cancer mortality was also significantly more elevated in the east-coast cohort when compared with the regional rates (SIR, 1.17; 95% CI, 1.00–1.36). Dietary information showed modest differences in consumption of fatty fish between the east and west coasts. In a recent update extending the follow-up until 2002 (Mikoczy & Rylander, 2009) expected mortality and cancer incidence were based on national

Table 2.5 Cohort studies of risk of cancer associated with high dietary intake of PCBs

Reference, location, follow-up period	Total subjects	Exposure assessment/ population	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Mikoczy & Rylander (2009) Sweden 1968–2002 (east coast) 1965–2002 (west coast)	2042 (east coast) and 6674 (west coast) fishermen's wives	Dietary intake of fatty fish from Baltic Sea (east coast)		Comparison with national rates		*SIR (95% CI)*	Age Possible coexposure to PCDDs and PCDFs
		West coast	All sites		1201	0.92 (0.87–0.98)	
			Stomach		39	0.86 (0.61–1.18)	
			Colon		103	0.97 (0.79–1.18)	
			Rectum		52	1.00 (0.75–1.31)	
			Liver, bile ducts		39	0.99 (0.70–1.36)	
			Lung		33	0.61 (0.42–0.86)	
			Breast		305	0.90 (0.81–1.01)	
			Melanoma		38	1.03 (0.73–1.41)	
			Skin		60	1.43 (1.09–1.84)	
			Brain		41	1.05 (0.75–1.42)	
			Soft tissue sarcoma		3	0.38 (0.08–1.10)	
			Lymphohaematopoietic (200–207)		75	0.92 (0.73–1.16)	
			Hodgkin lymphoma (201)		3	0.63 (0.13–1.83)	
			Multiple myeloma (203)		19	1.12 (0.68–1.76)	
			NHL (200, 202)		35	1.03 (0.71–1.43)	
		East coast	All sites (140–209)		345	1.09 (0.98–1.21)	
			Stomach		12	1.39 (0.72–2.43)	
			Colon		38	1.61 (1.14–2.21)	
			Rectum		13	1.09 (0.58–1.86)	
			Liver, bile ducts		11	1.35 (0.67–2.42)	
			Lung		12	0.83 (0.43–1.46)	
			Breast		92	1.03 (0.83–1.27)	
			Melanoma		8	0.76 (0.33–1.49)	
			Skin		9	0.95 (0.43–1.80)	
			Brain		14	1.37 (0.75–2.30)	
			Soft tissue sarcoma		1	0.51 (0.01–2.84)	
			Lymphohaematopoietic (200–207)		18	0.94 (0.56–1.48)	
			Hodgkin lymphoma (201)		1	0.93 (0.02–5.19)	
			Multiple myeloma (203)		6	1.58 (0.58–3.43)	
			NHL (200, 202)		6	0.71 (0.26–1.55)	

Table 2.5 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment/ population	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Turunen *et al.* (2008) Finland 1980–2005	4260 fishermen's wives	Dietary intake of fatty fish from Baltic Sea		Overall, compared with national death rates		*SMR (95% CI)*	Age
			All malignant neoplasms		115	0.97 (0.80–1.15)	
			Colon		10	1.30 (0.62–2.39)	
			Rectum & anus		8	2.13 (0.92–4.19)	
			Stomach		2	0.30 (0.04–1.08)	
			Breast		18	0.80 (0.47–1.25)	
			Larynx, trachea & lung		8	0.70 (0.30–1.38)	
			Lymphoid, haematopoietic, & related tissue		10	0.83 (0.40–1.53)	
Helmfrid *et al.* (2012) Gusum, Sweden 1960–2003	Residents in contaminated area (number not given)	Consumption of foods with high PCB content from contaminated local river	(ICD-7)	Overall, compared with national death rates		*SIR (95% CI)*	Age, time period Possible coexposure to metals because of industrial activities
		Men	All sites		346	0.91 (0.78–1.05)	
			Stomach		25	1.00 (0.65–1.83)	
			Colon		21	0.76 (0.46–1.16)	
			Rectum		10	0.54 (0.25–0.99)	
			Liver/bile ducts		8	0.88 (0.37–1.73)	
			Pancreas		14	1.17 (0.63–1.97)	
			Bronchus & lung		22	0.64 (0.40–0.97)	
			Breast		1	NR	
			Prostate		100	1.06 (0.86–1.29)	
			Testis		7	2.46 (0.99–5.08)	
			Malignant melanoma of skin		15	1.56 (0.87–3.94)	
			Other skin		15	0.81 (0.45–1.34)	
			Brain		3	0.31 (0.06–0.91)	
			Lymphoma (200–202)		22	1.60 (1.00–2.42)	
			Multiple myeloma (203)		7	1.25 (0.50–2.42)	
			Leukaemia (204)		5	0.88 (0.28–3.57)	
			Lymphatic & haematopoietic tissues (200–207)		38	1.20 (0.84–1.65)	

Table 2.5 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment/ population	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Helmfrid et al. (2012) Gusum, Sweden 1960–2003 (cont.)		Women	All sites		295	0.91 (0.77–1.07)	
			Stomach		15	1.11 (0.62–1.88)	
			Colon		17	0.65 (0.37–1.04)	
			Rectum		12	0.95 (0.49–1.66)	
			Liver/bile ducts		9	0.91 (0.41–1.73)	
			Pancreas		6	0.62 (0.22–1.34)	
			Bronchus & lung		6	0.49 (0.18–1.08)	
			Breast		80	0.97 (0.77–1.21)	
			Malignant melanoma of skin		11	1.22 (0.60–2.19)	
			Other skin		7	0.70 (0.28–1.44)	
			Brain		13	1.37 (0.72–2.34)	
			Lymphoma (200–202)		8	0.82 (0.35–1.63)	
			Multiple myeloma (203)		2	0.49 (0.05–1.77)	
			Leukaemia (204)		4	1.25 (0.34–3.21)	
			Lymphatic & haematopoietic tissues (200–207)				
Tomasallo *et al.* (2010) Great Lakes area, USA 1995–2006	3757 subjects (2275 fish consumers, 1482 non-consumers)	Dietary intake of Great Lakes sport fish				*SMR (95% CI)*	
			All cancers	Fish consumers	83	0.92 (0.74–1.13)	
			Pancreas		6	1.24 (0.45–2.44)	
			Brain		5	1.91 (0.60–3.96)	
			Breast, ovary, & uterus		6	1.47 (0.46–3.04)	
			All cancers	Non-consumers	47	0.87 (0.64–1.13)	
			Pancreas		2	0.72 (0.07–2.07)	
			Brain		1	0.70 (0.0–2.76)	
			Breast, ovary, & uterus		1	0.44 (0.0–1.73)	

NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; SIR, standardized incidence ratio; SMR, standardized mortality ratio

rates, and no direct comparison between east- and west-coast cohorts were reported. Standardized mortality ratios for all cancers combined were 0.98 (0.91–1.06) for the west-coast cohort and 1.15 (95% CI, 0.98–1.34) for the east-coast cohort. Statistically significant excess incidence was reported for cancer of the colon in the east-coast cohort (SIR, 1.61; 95% CI, 1.14–2.21) and non-melanoma cancer of the skin in the west-coast cohort (SIR, 1.43; 95% CI, 1.09–1.84). [The Working Group noted that the excess of cancer incidence observed using regional rates as reference became nonsignificant when national rates were used. Because of the lack of specific exposure information, the possibility of confounding cannot be ruled out.]

In Finland, a cohort of Baltic Sea fishermen was identified from the Professional Fishermen Register, and their wives were identified from the Population Register (Turunen *et al.*, 2008). A cohort of 4260 women was linked with Statistics Finland's national cause-of-death data from 1980 to 2005, and expected deaths were calculated according to national rates. Furthermore, a cross-sectional substudy was conducted among 94 cohort participants who undertook a health examination in 2004–2005, including a food-frequency questionnaire and fasting-blood collection; data from a population-based survey were used for comparison. No statistically significant standardized mortality ratios were found for all cancers, or for any specific tumour site.

After an accidental spill of oil contaminated with PCBs from the brass works industry in Gusum, Sweden, in 1972, elevated levels of PCBs were measured in local fish in 2006. Among the population of the contaminated area, 641 cases of cancer were identified in 1960–2003, which was not above the expected number based on national rates for the same period (Helmfrid *et al.*, 2012). Among men, 22 lymphomas were observed, with a statistically significant increased standardized incidence ratio (SIR) of 1.60 (95% CI, 1.00–2.42). There was also an increased risk of cancer of the testis (SIR, 2.46; 95% CI, 0.99–5.08; seven cases) and malignant melanoma of the skin (SIR, 1.56; 95% CI, 0.87–3.94) in the contaminated area when compared with the general population, while the risk for cancer of the prostate was near unity (SIR, 1.06; 95% CI, 0.86–1.29). In addition to the cohort analysis, a case–control study based upon a dietary questionnaire was carried out on 67 cases of cancer, including cancers of the colorectum, skin (including melanoma), cervix, breast, prostate, and lymphoma, and 326 controls resident in the same area. The case–control analysis reported an increased risk of cancer of the female breast associated with consumption of fish more than twice per month, but with only two cases. Excess risks of lymphoma (five cases, including men and women) were also observed with consumption of fish more than twice per month. Consumption of locally produced foods was also analysed, but no other statistically significant increased risks associated with potential sources of exposure to PCBs were reported in the case–control analysis. [The Working Group noted that subjects from this area could have also been exposed to other contaminants, such as metals. The case–control analysis was based upon a very small number of subjects, and there was poor assessment of dietary exposure and control for potential confounders.]

Regular consumption of predatory fish constitutes a large source of exposure to several persistent pollutants, including PCBs, for residents of the Great Lakes Basin (Falk *et al.*, 1999). A cohort of regular consumers of sport fish from the Great Lakes, and residents in the same communities who consumed no sport fish from the Great Lakes (referents), were recruited in 1993–94 (Tomasallo *et al.*, 2010). A total of 3757 subjects (2275 fish consumers and 1482 referents) were followed from 1995 to 2006, and mortality was compared with national death rates. Information about fish consumption and other lifestyle characteristics was obtained by telephone interview, and a blood sample for measurement of PCBs

was collected for a subgroup of 610 individuals. During the 12-year follow-up period, 342 deaths were recorded, including 134 deaths from cancer. Cancer mortality rates did not differ from those of the general population for fish consumers or referents: SMRs for all cancers were 0.92 (95% CI, 0.74–1.13) and 0.87 (95% CI, 0.64–1.13), respectively. However, fish consumers had non-statistically significant excesses of cancers of the pancreas, brain and combined breast, uterus and ovary. Although blood PCB levels were positively associated with fish consumption among fish consumers ($P < 0.001$ for comparison of mean PCB concentrations according to three levels of fish consumption), there was no association between fish consumption and cancer mortality. [The Working Group regarded this study as informative because it included information about PCB exposures, as well as fish consumption. However, the possibility of confounding from concurrent exposure to other contaminants could not be ruled out.]

[Compared with cohorts of Yusho or Yucheng patients, who consumed food contaminated with a high level of PCBs for a short period, potential exposure to PCBs through diet is a long-term, low-level exposure. Fish or local vegetables contaminated by PCBs are often also contaminated by other compounds such as DDT, PCDFs, PCDDs, or heavy metals. Furthermore, as detailed information on other risk factors for the tumours analysed (i.e. lymphoma, breast, colon, skin) was lacking, residual confounding could not be ruled out as a potential explanation for the associations found in these studies.]

2.2.3 Nested case–control studies of PCB concentrations in blood or adipose tissue

Since the 1980s, several cohort studies have addressed the potential relationship between risk of cancer and internal measurements of exposure to PCBs. The most commonly used marker of past exposure to PCBs is the serum or plasma concentration of a set of PCB congeners, although a few studies have measured PCB concentrations in adipose tissue. Most studies used a case–control design nested within a cohort as an efficient method for analysis: PCB concentrations were measured in all incident cases diagnosed within a defined follow-up period, and in a sample of at-risk subjects (controls) selected within the same cohort. A few studies have used a case–cohort approach, in which the referent group is formed by a random sample of the whole cohort selected at baseline. Various sets of PCB congeners were measured; PCB-118, PCB-138, PCB-153, and PCB-180 were reported more often because they were frequently analysed and prevalent in human biological samples (see Section 1.2 for more information on analytical methods). In some instances results for individual congeners were provided but, unless otherwise specified, the summary estimate refers to the sum of all measured PCBs.

(a) Cancer of the breast

See Table 2.6

(i) USA

The New York University Women's Health Study (NYUWHS) enrolled 14 290 women from New York City between 1985 and 1991; these women donated a 30 mL blood sample while attending a mammography screening clinic (Wolff *et al.*, 1993). During this period, women who were diagnosed with cancer of the breast 1–6 months after entry into the study were defined as cases. Controls were selected at random from all cohort members who were alive and free of cancer at the time of the cancer diagnosis in a case patient, matched on menopausal status, age at entry and day of menstrual cycle at the time of blood collection. Concentrations of PCBs were measured without correction for serum lipids. [Since cases were diagnosed only 1–6 months subsequent to entry, the disease

Table 2.6 Nested case-control studies on risk of cancer of the breast and measured serum or adipose concentrations of PCBs

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
USA							
Wolff *et al.* (2000a) New York, USA 1985–1991 until 1994	14 275 women; 148 cases and 295 controls	Serum, GC, lipid-corrected concentrations (Akins method)		Quartiles of PCB concentration (ng/g lipid)			Age, menopausal status, date of blood collection (matching), age at menarche, number of pregnancies, age at first pregnancy, family history of breast cancer, lactation, height, BMI No. and list of PCB congeners not provided; LOD, < 1 ng/mL
				478–638	30	1.55 (0.59–4.12)	
				639–876	26	1.23 (0.49–5.08)	
				> 876	33	2.02 (0.76–5.37)	
						P for trend = 0.23	
Krieger *et al.* (1994) Northern California, USA 1964–1969 until 1990	57 040 women; 150 case–control pairs (50 each white, black, Asian)	Serum, GC/ECD, no lipid adjustment		Tertiles of PCB concentration (ng/mL)			Race, age, date of entry, duration of follow-up (matching), BMI, age at menarche, menopausal status, ever pregnant No. and list of PCB congeners not provided; LOD, 2 ng/mL
			All women	3.5–5.0		1.17 (0.66–2.10)	
				5.1–20.6		0.94 (0.48–1.84)	*P* for trend = 0.88
			White	2.94–3.96		0 21 (0.05–0.88)	
				3.97–10.01		0 17 (0.03–0.89)	*P* for trend = 0.039
			Black	3.51–4.98		1.74 (0.56–5.43)	
				4.99–20.55		2 13 (0.70–6.50)	*P* for trend = 0.18
			Asian	4.16–5.76		1.56 (0.47–5.17)	
				5.77–14.62		1.06 (0.32–3.52)	*P* for trend = 0.93
Hunter *et al.* (1997), Laden *et al.* (2001a) 11 states, USA (Nurses' Health Study cohort) 1989–1994	32 826 women; 370 case–control pairs	Serum PCB levels measured by GC/ECD, no lipid adjustment		Quintiles of PCB concentration (µg/g lipid)			Age, menopausal status, month of blood collection, fasting status at blood sampling (matching), BMI, breast cancer in first-degree relatives, history of benign breast disease, age at menarche, first full term pregnancy, parity, lactation LOD, < 1 ng/mL; sum of 16 penta-, hexa-, and heptachlorobiphenyls; congeners 118, 138, 153 and 180 accounted for 64% of total
			Sum of PCBs	0.406–0.491	65	0.73 (0.44–1.21)	Continuous (log-concentration) *P* = 0.56
				0.491–0.596	65	0.75 (0.44–1.28)	
				0.602–0.763	80	0.85 (0.49–1.47)	
				0.766–1.986	74	0.84 (0.47–1.52)	

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Hunter et al. (1997), Laden et al. (2001a) (cont.)			PCB-118	0.045–0.060	62	0.68 (0.39–1.17)	Continuous (log-concentration) $P = 0.67$
				0.061–0.074	61	0.62 (0.36–1.06)	
				0.074–0.101	90	1.02 (0.59–1.77)	
				0.101–0.313	69	0.69 (0.39–1.22)	
			PCB-138	0.066–0.087	69	0.82 (0.49–1.37)	Continuous (log-concentration) $P = 0.21$
				0.087–0.108	75	0.90 (0.53–1.50)	
				0.109–0.142	65	0.71 (0.41–1.20)	
				0.143–0.402	78	0.87 (0.50–1.50)	
			PCB-153	0.078–0.094	58	0.67 (0.39–1.14)	Continuous (log-concentration) $P = 0.26$
				0.095–0.121	75	0.69 (0.41–1.15)	
				0.121–0.159	69	0.77 (0.45–1.31)	
				0.159–0.447	79	0.83 (0.47–1.48)	
			PCB-180	0.055–0.068	65	0.70 (0.41–1.20)	Continuous (log-concentration) $P = 0.67$
				0.069–0.082	62	0.65 (0.37–1.11)	
				0.082–0.103	63	0.70 (0.41–1.19)	
				0.103–0.467	91	0.98 (0.55–1.75)	
				Tertiles of PCB concentration			
			BMI ≥ 30	Tertile 2	19/21	0.40 (0.15–1.05)	Continuous (log-concentration) $P = 0.02$
				Tertile 3	11/19	0.26 (0.09–0.76)	
			Nulliparous	Tertile 2	5/14	0.81 (0.18–3.68)	Continuous (log-concentration) $P = 0.02$
				Tertile 3	12/6	5.30 (1.06–26.6)	
Laden *et al.* (2002) 1989–1994	367 pairs	Serum PCB levels measured by GC/ECD, no lipid adjustment	*CYP1A1* exon 7 genotype	Tertiles of PCB concentration			Same data set as study by Hunter *et al.* (1997), Laden *et al.* (2001a)
			Wildtype	0.13–0.46	113	1.00	
			Variant	0.13–0.46	12	0.54 (0.24–1.22)	
				0.46–0.65	18	0.76 (0.35–1.63)	
				0.65–1.99	21	1.36 (0.60–3.12)	Interaction ($P = 0.19$)
			Postmenopausal women				
			Wildtype	0.13–0.47	84	1.00	
			Variant	0.13–0.47	16	0.52 (0.20–1.36)	
				0.47–0.67	12	1.29 (0.51–3.21)	
				0.67–1.99	7	2.78 (0.99–7.82)	Interaction ($P = 0.05$)

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Dorgan *et al.* (1999) Missouri, USA 1977–1987 until 1989	7224 women; 105 cases and 208 matched controls	Serum, GC/ECD, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)			Age, benign breast disease, mo/year blood collection (matching), height, weight, BMI, parity, age at menarche, menopause, estrogen use, history of breast cancer in first-degree relatives, smoking, education 70% lost to follow-up after 1983; LOD, 0.25–0.97ng/g; 27 PCB congeners measured[a]
			Sum of PCBs	258–369	21	0.7 (0.3–1.4)	Continuous (log-concentration) $P = 0.79$
				370–563	33	1.1 (0.6–2.2)	
				564–2682	21	0.7 (0.3–1.5)	
			PCB-118	50–74	25	1.1 (0.6–2.3)	Continuous (log-concentration) $P = 0.77$
				75–109	34	1.6 (0.8–3.2)	
				110–533	23	1.0 (0.5–2.2)	
			PCB-138	70–93	29	1.3 (0.6–2.5)	Continuous (log-concentration) $P = 0.82$
				94–124	26	1.2 (0.6–2.3)	
				125–359	26	1.2 (0.6–2.4	
Helzlsouer *et al.* (1999) Maryland, USA 1974–1994 or 1989–1994	20 305 recruited in 1974; 25 080 recruited in 1989; 340 cases and matched controls	Serum, GC/ECD, lipid-corrected concentrations		Sum of PCBs (ng/g lipid)			Age, race, menopausal status, date of blood collection
			Recruited in 1974	< 394.47	42	1.00	Approx. 70% participation; no association for specific congeners (data not reported); no effect modification by menopausal status, ER status, polymorphisms in *GSTM1*, *GSTT1*, *GSTP1*, *COMT* and *CYP17*; LOD, NR; 27 PCB congeners measured
				394.48–558.72	59	1.41 (0.79–2.50)	
				558.73–669.46	41	0.94 (0.49–1.77)	
				669.47–852.22	45	1.08 (0.59–2.01)	
				852.23–6460.04	48	1.12 (0.59–2.15)	P for trend = 0.44
			Recruited in 1989	13.6–191.8	40	1.00	
				191.9–333.5	32	0.78 (0.41–1.47)	
				333.6–2007.9	33	0.76 (0.38–1.51)	P for trend = 0.60

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cohn *et al.* (2012) Oakland, California, USA 1959–1967 until 1998 (average follow-up, 17 years)	Women in the CHDS who gave birth in 1959–1967 [number of participants not given]; 112 case–control pairs (cases all aged < 50 yr)	Serum samples collected during early post-partum, GC/ECD		Quartiles of PCB concentration (mmol/L)			Age (matching), blood lipids (total cholesterol, total triglycerides), parity, year of blood draw, BMI, breast-feeding after current pregnancy 10 congeners measured[b] No associations with total PCBs or with Wolff's groups (data not shown)
			PCB-167	Quartile 2	NR	1.09 (0.48–2.47)	*P* for trend < 0.04
				Quartile 3	NR	0.70 (0.27–1.78)	
				Quartile 4	NR	0.24 (0.07–0.79)	
			PCB-187	Quartile 2	NR	0.94 (0.41–2.17)	*P* for trend < 0.02
				Quartile 3	NR	0.92 (0.36–2.38)	
				Quartile 4	NR	0.35 (0.11–1.14)	
			PCB-203	Quartile 2	NR	1.21 (0.46–3.18)	*P* for trend < 0.001
				Quartile 3	NR	2.89 (0.98–8.55)	
				Quartile 4	NR	6.34 (1.85–21.7)	
Northern Europe							
Høyer *et al.* (1998, 2000) Copenhagen, Denmark (CCHS cohort) 1979–1993	5838 women with two examinations (1976–78 and 1981–83); 155 cases, 274 controls	Serum, GC/ECD, lipid-corrected concentrations		Quartiles of PCB concentration [unit not given]			Age, date of examination, weight changes between two examinations, parity, HRT Response rate 75% (first exam), 78% (second exam); LOD, 0.66–0.20 ng/mL; No. and list of PCB congeners not provided
			Sum of PCBs	Quartile 2	NR	0.8 (0.4–1.9)	
				Quartile 3	NR	0.8 (0.4–1.7)	
				Quartile 4	NR	1.6 (0.8–3.3)	*P* for trend = 0.17
			PCB-118	Quartile 2	NR	0.8 (0.4–1.9)	
				Quartile 3	NR	1.1 (0.5–2.4)	
				Quartile 4	NR	1.9 (0.9–3.9)	*P* for trend = 0.07

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Høyer et al. (1998, 2000) (cont.)			PCB-138	Quartile 2	NR	0.9 (0.4–1.9)	
				Quartile 3	NR	1.0 (0.5–2.1)	
				Quartile 4	NR	2.1 (1.0–4.4)	*P* for trend = 0.04
			PCB-153	Quartile 2	NR	0.7 (0.3–1.4)	
				Quartile 3	NR	0.8 (0.4–1.8)	
				Quartile 4	NR	1.3 (0.2–2.6)	
			PCB-180	Quartile 2	NR	1.2 (0.6–2.5)	
				Quartile 3	NR	1.1 (0.5–2.2)	
				Quartile 4	NR	0.9 (0.4–2.2)	
Høyer *et al.* (2001)	161 cases, 318 controls		ER status	Quartiles of PCB concentration [unit not given]			Age, weight, parity, HRT See Høyer *et al.* (2000) for details
			ER+	811–1076.04	24/56	1.1 (0.6–1.7)	
				1076.04–1405.73	20/57	0.7 (0.4–1.2)	
				< 1405.73	36/56	1.3 (0.8–2.2)	
			ER–	811–1076.04	11/23	1.0 (0.4–2.7)	
				1076.04–1405.73	11/23	1.3 (0.4–3.9)	
				< 1405.73	8/23	0.8 (0.3–2.6)	
Høyer *et al.* (2002)	162 cases, 316 controls		*p53* mutations in tumour	Quartiles of PCB concentration [unit not given]			Age, weight, parity, HRT See Høyer *et al.* (2000) for details
			Wildtype	Quartile 2	24	0.53 (0.28–1.04)	
				Quartile 3	20	0.52 (0.26–1.05)	
				Quartile 4	34	0.96 (0.50–1.83)	
			≥ 1 p53 mutations	Quartile 2	9	1.78 (0.43–7.41)	
				Quartile 3	11	3.82 (0.85–17.4)	
				Quartile 4	10	3.00 (0.66–13.6)	

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Ward *et al.* (2000) Norway (Janus cohort) 1973–1991	25 431 women working outside home and resident on a farm; 150 case–control pairs	Serum, HRGC/ID-HRMS, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)		[95% CI not given]	Age (matching), occupation, age at first birth, parity, residence All cases ≥ 2 years from blood collection to diagnosis; sum of 36 congeners: 26 with > 90% samples > LOD Groups according to Wolff's classification (Wolff *et al.*, 1997)
			Sum of PCBs	Quartile 2		0.6	*P* = 0.47 (paired t-test)
				Quartile 3		0.8	
				Quartile 4		0.5	
			Group 1B	Quartile 2		0.6	*P* = 0.56 (paired t-test)
				Quartile 3		0.6	
				Quartile 4		0.5	
			Group 2A	Quartile 2		0.8	*P* = 0.50 (paired t-test)
				Quartile 3		0.6	
				Quartile 4		0.6	
			Group 2B	Quartile 2		0.4	*P* = 0.32 (paired t-test)
				Quartile 3		1.0	
				Quartile 4		0.5	
			Group 3	Quartile 2		0.7	
				Quartile 3		0.8	
				Quartile 4		0.6	*P* = 0.18 (paired t-test)
Raaschou-Nielsen *et al.* (2005) Copenhagen and Aarhus, Denmark (DCH cohort) 1993–1997 until 2000	29 875 women; 220–365 pairs, depending on congener	Adipose tissue, GC/MS, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)			Age, use of HRT (matching), benign breast tumour, BMI, alcohol, parity, age at delivery, years of HRT, lactation Response rate, 37%; all cases were postmenopausal women; LOD, 2.8–28.4 ng/g lipids; 18 PCB congeners[c] measured
			All cases (*n* = 365)	671–852	NR	0.9 (0.6–1.4)	
				852–1.024	NR	0.7 (0.5–1.1)	
				1024–4357	NR	1.1 (0.7–1.7)	
				Continuous (log ng/g lipid)	NR	*P* = 0.44	

Table 2.6 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Raaschou-Nielsen et al. (2005) (cont.)			ER+ (n = 261)	671–852	NR	1.1 (0.6–1.8)	
				852–1.024	NR	0.8–0.5–1.4)	
				1024–4357	NR	1.4 (0.8–2.5)	
				Continuous (log ng/g lipid)	NR	P = 0.50	
			ER– (n = 75)	671–852	NR	0.4 (0.1–1.3)	
				852–1.024	NR	0.3 (0.1–0.9)	
				1024–4357	NR	0.3 (0.1–0.9)	
				Continuous (log ng/g lipid)	NR	P = 0.007	

[a] Congeners measured: 28, 52, 56, 66, 74, 90, 101, 105, 110, 118, 138, 146, 153, 156, 170, 172, 178, 180, 183, 187, 189, 193, 194, 195, 201, 203, 206

[b] Congeners measured: 101, 187, 201, 138, 170, 99, 153, 180, 183, 203

[c] Congeners measured: 28, 52, 54, 99, 101, 104, 105, 118, 128, 138, 153, 155, 156, 170, 180, 183, 187, 201

BMI, body mass index; CHDS, Child Health and Development Studies; DCH, Diet, Cancer, and Health; ECD, electron capture detection; ER, estrogen receptor; FTP, full-term pregnancy; GC, gas chromatography; HRGC, high-resolution gas chromatography; HRT, hormone-replacement therapy; ID-HRMS, isotope dilution high-resolution mass spectrometry; LOD, limit of detection; mo, month; NR, not reported; PCB, polychlorinated biphenyl

could have been present when the blood sample was collected, despite negative mammography findings, and could therefore have affected the measured concentration of PCBs.] Additional cases and controls were included in an extended follow-up of this cohort to 1994, giving totals of 148 cases and 295 controls (Wolff *et al.*, 2000a). In this update, only incident cases were considered (thus excluding those with a lag time of 6 months or less). Serum lipids were measured and PCB concentrations were calculated on a lipid basis. The risk estimates were further adjusted for family history of cancer of the breast, reproductive risk factors, height, and body mass index (BMI). Odds ratios increased across quartiles of serum PCB concentrations, reaching 2.02 (95% CI, 0.76–5.37) in the highest quartile; the trend was not statistically significant. [The Working Group noted that this was a well-designed study; however, the follow-up was relatively short and the analysis thus had limited power.]

Krieger *et al.* (1994) performed a nested case–control study among women in Northern California, USA, who were members of the Kaiser Permanente Medical Care Program and who underwent a health examination, including giving a sample of blood, between 1964 and 1969, and were followed up until 1990. Among the 2072 patients identified with cancer of the breast, 150 cases were randomly selected (50 white, 50 black, and 50 Asian) and matched to 150 controls by race, age, date of entry, and date of follow-up. After adjustment for reproductive factors, menopausal status and BMI, no association was seen between risk of cancer of the breast and serum PCB concentrations for all subjects (OR, 0.93; 95% CI, 0.83–1.05 per ppb). In subgroup analyses by ethnic group, there was an inverse association for white women (OR, 0.21; 95% CI, 0.05–0.88; and OR, 0.17; 95% CI, 0.03–0.89 for the second and third tertiles respectively, *P* for trend = 0.04) and a positive association for black women (OR, 1.74; 95% CI, 0.56–5.43 and OR, 2.13; 95% CI, 0.70–6.50, respectively, *P* for trend = 0.18). [This was a well-designed study with adjustment for relevant confounders, with more than 2000 cases of cancer of the breast identified during the follow-up; however, only 150 were selected for measurement of PCBs and thus power was limited, especially for subgroup analyses.]

The Nurses' Health Study was established in 1976 and included more than 120 000 registered nurses in the USA, who were subsequently followed by questionnaire every 2 years and 32 826 women from the cohort provided a blood sample between 1989 to 1990. Results were reported from follow-ups until 1992 (Hunter *et al.*, 1997) and 1994 (Laden *et al.*, 2001a). In the first follow-up, no association was found between cancer of the breast and PCB concentrations after adjustment for family history of cancer of the breast, reproductive factors, BMI, and cholesterol (Hunter *et al.*, 1997). The extended follow-up to 1994 included 370 case–control pairs, and provided results for individual congeners (Laden *et al.*, 2001a). The pattern of risk by quintile did not change and no association was found for PCB-118, PCB-138, PCB-153, or PCB-180. In subgroup analyses, a significant increase in risk was reported for exposure to the sum of 16 PCBs in nulliparous women (OR, 5.30; 95% CI, 1.06–26.6 for the third tertile of PCB serum concentrations when compared with the first tertile, but the overall trend was not significant; $P = 0.11$). An inverse association was found for women with BMI ≥ 30; the odds ratio for the highest versus lowest tertile was 0.26 (95% CI, 0.09–0.76; *P* for trend = 0.01), while elevated odds ratios were found for women in the highest tertile of PCB exposure with BMI of 25–29.9 and < 25. Since PCB exposure induces activity of cytochrome P450 1A1 (CYP1A1), and PCBs themselves can be metabolized to carcinogenic intermediates by this enzyme, it was explored whether the potential effect of PCBs was modified by the CYP1A1 polymorphism using the same data set (Laden *et al.*, 2002). In 367 case–control pairs, *CYP1A1* exon 7 and *MspI* polymorphisms

were determined. The relative risk increased across tertiles of PCB exposure among those with the variant exon 7 genotype, but not among those with the wild-type genotype. When the analysis was restricted to postmenopausal women, the odds ratio was 2.78 (95% CI, 0.99–7.82) for the highest tertile of PCB exposure, with a *P* value for interaction of 0.05. No gene–environment interaction was seen for *MspI* polymorphism. [The Working Group noted that this was a well-designed study with good controls for most relevant confounders, including reproductive factors and family history of cancer of the breast. The sample size was reasonable when compared with previous studies, and estimates for specific PCB congeners were reported. The only statistically significant associations were limited to specific subgroups after several subgroup analyses and multiple comparisons.]

In another study in the USA, 7224 female volunteers were identified through the Breast Cancer Detection and Demonstration Project (BCDDP) and donated blood to the Columbia Missouri Breast Cancer Serum Bank; active follow-up continued until 1989 (Dorgan *et al.*, 1999). Among these women, 105 were diagnosed with histologically confirmed cancer of the breast, and two controls for each were selected, matched on year of age, date of blood sampling, and history of benign breast disease at the time of enrolment. No association was reported between risk of cancer of the breast and lipid-corrected concentrations of total PCBs (sum of 27 PCB congeners measured), or serum concentrations of PCB-118 and PCB-138, after adjustment for the main risk factors for cancer of the breast. [This study had a relatively small number of cases and was therefore of limited power].

A case–control study was conducted among residents of Washington County, Maryland, USA, who had participated in one of two studies conducted in 1974 and 1989 to obtain blood samples for a serum bank (Helzlsouer *et al.*, 1999). Participants were followed up until 1994 by linkage with the Washington County Cancer Registry. Of the 346 cases of cancer of the breast diagnosed, valid measurements of PCBs were available for 340 cases, which were matched to 340 participating women without cancer of the breast by age, menopausal status and date of blood collection. Taking into account relevant confounders including family history of cancer of the breast, reproductive history and BMI, no association was found with total PCB serum concentration or with specific congeners. There were no statistically significant associations after stratifying for menopausal status, estrogen-receptor (ER) status or polymorphism in *GSTM1*, *GSTT1*, *GSTP1*, *COMT*, or *CYP17*. [The Working Group noted that this study, with an analysis adjusting for most relevant confounders, investigated the hormone-receptor status of tumours, and also considered possible effect modification by polymorphisms in several genes with a role in metabolism. Although the sample size was adequate for the main analysis, it was limited for subgroup analyses.]

A nested case–control study compared serum concentrations of 16 PCBs in archived early-postpartum serum samples collected between 1959 and 1967 from 112 cases of cancer of the breast and 112 age-matched controls (Cohn *et al.* 2012). Subjects were residents of Oakland, California, participating in the Child Health and Development Studies. Cases of cancer of the breast were identified by linkage to the California Cancer Registry, and the California Vital Status Records. The median time from blood draw to diagnosis was 17 years, and mean age of cases at diagnosis was 43 years. No associations were reported between risk of cancer of the breast and sum of total PCBs, or with PCB groups (Wolff *et al.*, 1997). [No odds ratios were reported for these analyses]. PCB-167 was associated with a lower risk (OR for highest versus lowest quartile, 0.2; 95% CI, 0.1–0.8), as was PCB-187 (OR for highest versus lowest quartile, 0.4; 95% CI, 0.1–1.1). In contrast, PCB-203 was associated

with an increased risk (OR for highest versus lowest quartile, 6.3; 95% CI, 1.9–21.7). [This was the only nested case–control study to include mostly premenopausal women. The study had limited power.]

(ii) Northern Europe

Serum samples were obtained in 1976 from a cohort of 7712 women aged 20 years or older who participated in the Copenhagen City Heart Study (Denmark) and provided information and a non-fasting blood sample (Høyer *et al.*, 1998). Case ascertainment was achieved by linkage to the Danish Cancer Registry up to 1993. For each case, two women free of breast cancer and alive at the time of diagnosis and matched for age and date of examination were selected from the rest of the cohort. After excluding subjects without a valid serum sample, 240 cases and 447 controls were included in the study. Concentrations of 28 PCB congeners were measured in serum. No association was reported between risk of cancer of the breast and lipid-adjusted concentrations of the sum of PCBs or specific congeners.

Participants in the same cohort study were invited for a second examination 5 years after recruitment; 155 cases and 274 controls from the previous study had a second serum sample available (Høyer *et al.*, 2000). Analyses were carried out in this group for four common PCB congeners. A statistically significant increased risk and trend was found for subjects in the highest quartile of PCB-138 concentration (average of two measurements; OR, 2.1; 95% CI, 1.0–4.4; *P* for trend = 0.04). Elevated odds ratios were reported for the highest quartile of exposure to total PCBs and congeners PCB-118 and PCB-153 (OR, 1.6, 1.9 and 1.3, respectively), but the association was not significant for these congeners or for PCB-180.

Within the same cohort, a total of 161 cases with ER status information and 318 matched controls who were free of breast cancer were included in an analysis according to ER status (Høyer *et al.*, 2001). No association was found between incidence of cancer of the breast and PCB concentrations regardless of ER status. Finally, paraffin embedded tumour-tissue specimens were retrieved for 162 cases and 316 controls and found to be suitable for *p53* analysis (Høyer *et al.*, 2002). A non-significant increased risk of cancer of the breast (OR, 3.00; 95% CI, 0.66–13.62) was observed in the highest level of exposure to PCBs among women with mutant *p53*. [Several analyses were carried out using data from this Danish study, but power was limited, particularly for subgroups.]

The JANUS Serum Bank contains serum samples collected between 1973 and 1991 from almost 300 000 individuals undergoing routine health examinations in Norway. Cases of cancer of the breast were identified among 25 431 women working outside home and resident on a farm who were followed until 1993 through linkage with the Norwegian Cancer Registry (Ward *et al.*, 2000). From the 272 cases diagnosed during this period, 150 women with a blood sample taken 2 or more years before diagnosis were randomly selected; an equal number of controls were matched to cases by date of sample collection and date of birth. The mean lipid-corrected concentration of serum PCBs (sum of 36 congeners) was similar for cases and controls (*P* value, 0.47 for paired *t*-test). No association was found for specific PCB congeners or for PCB groups as defined by Wolff *et al.* (1997). [The Working Group noted that this study was well designed and considered most relevant confounders for cancer of the breast but, similar to other nested case–control studies with serum PCB measurements, had limited power.]

Between 1993 and 1997, 29 875 Danish women aged 50 to 64 years were enrolled in a prospective study of diet and cancer and followed until December 2000 through linkage with Danish Cancer Registry (Raaschou-Nielsen *et al.*, 2005). During this period, 409 women were diagnosed with postmenopausal cancer of the breast; each case was matched to one control by age,

postmenopausal status (known/probable), and use of hormone replacement therapy, and measurements of 18 PCBs in adipose-tissue biopsies were obtained. No association was found between concentrations of PCBs and risk of cancer of the breast in the whole data set. However, an inverse association was observed when the analysis was restricted to the 75 ER-negative (ER–) cases (OR, 0.3; 95% CI, 0.1–0.9). This inverse association for ER– cases was also observed for the congeners PCB-138, PCB-153, PCB-170, PCB-180, PCB-183 and PCB-187. [The Working Group noted that this was the largest nested case–control study of cancer of the breast with PCB measurements, and the only one to measure PCBs in adipose tissue rather than serum. The inverse association of concentrations of total PCB and some PCB congeners among women with ER– tumours does not have a clear interpretation.]

(b) NHL

See Table 2.7

(i) USA

Seventy-four cases of NHL (ICD-8 200 or 202) identified during follow-up from 1975 to 1994 of the cohort from Washington County, Maryland, USA (described in the previous section) and 147 controls matched by race, sex, and age were included in a case–control study (Rothman *et al.*, 1997). PCB concentrations were measured in serum collected before diagnosis and corrected for lipids. There was a significant dose–response relationship between risk of NHL and quartiles of lipid-corrected serum concentrations of PCBs (sum of 28 measured congeners). The odds ratios for the third and fourth quartiles when compared with the first quartile were 2.8 (95% CI, 1.1–7.6) and 4.5 (95% CI, 1.7–12.0) respectively; these estimates were adjusted, in addition to matching variables, for education, cigarette smoking and occupational exposure to suspected risk factors for NHL. There was also an indication that seropositivity for the Epstein-Barr virus early antigen (EBV-EA) potentiated the effects of serum PCBs, with a statistically significant interaction (*P* value = 0.025).

An analysis of the same data set focusing on the effect of specific congeners reported a significant exposure–response relationship between risk of NHL and increasing concentrations of PCB-118, PCB-138, and PCB-153 (*P* for trend < 0.05) (Engel *et al.*, 2007). [The Working Group noted that this was the only nested case–control study on PCB concentrations and NHL that adjusted for occupational exposure to potential risk factors.]

An analysis of the association between NHL and exposure to PCBs conducted within the Nurses' Health Study cohort (described in the previous section) was reported in the same publication (Engel *et al.*, 2007). Thirty women with incident NHL diagnosed between the date of blood collection and May 1994 (median follow-up, 1 year) were included as cases and 78 cohort members selected previously as controls for a study of cancer of the breast served as controls. Plasma samples were analysed for PCB concentrations for cases and for controls at the same time. A statistically significant exposure–response relationship was observed between risk of NHL and increasing concentrations of lipid-corrected PCBs (sum of 21 congeners), with an odds ratio of 4.7 (95% CI, 1.2–18.9) for the third tertile, adjusted for age, BMI, and smoking status. A significant exposure–response relationship was also observed for PCB-118 and PCB-138 (*P* for trend < 0.05), but not for PCB-153.

An extended follow-up of the Nurses' Health Study cohort (median time to diagnosis, 5.8 years) included 145 cases of NHL and selected two controls for each case (n = 290) matched on age, race, month of blood draw, and fasting status (Laden *et al.*, 2010). Women with NHL were identified by annual follow-up questionnaires and confirmed by review of medical records and pathology reports. No association was observed between total serum concentrations of PCBs

Table 2.7 Nested case-control studies on risk of non-Hodgkin lymphoma and measured serum or adipose concentrations of PCBs

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
USA							
Rothman *et al.* (1997) Maryland, USA 1972–1990 until 1994	25 802 adults; 74 cases, 147 controls	Serum, GC/ECD, lipid-corrected concentrations		Quartiles of PCB concentration (ng/g lipid)			Race, sex, age (matching), education, cigarette smoking, potential for occupational exposure
			Sum of PCBs	648–806	13	1.3 (0.5–3.3)	28 congeners measured[a]
				814–1060	21	2.7 (0.9–7.8)	
				1070–2070	30	4.1 (1.7–11.9)	*P* for trend = 0.0008
Engel *et al.* (2007) Maryland, USA				Median of quartiles of PCB concentration (ng/g lipid)			Same population studied by Rothman *et al.* (1997) and Helzlsouer *et al.* (1999)
			Total PCBs	726.0	13	1.6 (0.6–4.3)	
				911.5	21	3.0 (1.1–8.3)	
				1337.5	30	4.6 (1.7–12.7)	
			PCB-118	124.6	23	4.9 (1.6–15.3)	
				164.9	17	3.5 (1.0–11.8)	
				214.7	29	5.4 (1.7–17.1)	*P* for trend < 0.05
			PCB-138	129.1	20	2.5 (0.9–6.5)	
				164.5	19	2.7 (1.0–7.5)	
				242.4	27	4.4 (1.5–12.6)	*P* for trend < 0.05
			PCB-153	122.4	14	1.0 (0.4–2.3)	
				163.2	17	1.4 (0.5–3.5)	
				246.9	27	2.2 (0.9–5.2)	*P* for trend < 0.05

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Laden *et al.* (2010) 11 states, USA (Nurses' Health Study cohort)	145 cases and 290 controls	Serum, GC/ECD, lipid-corrected concentrations		Median of quartiles of PCB concentration (ng/g lipid)			Race, age, date of and fasting status at blood draw (matching), region, BMI, smoking, height, parity, breastfeeding 51 congeners measured[a]
			Total PCB	547.8	41/73	1.25 (0.68–2.28)	Continuous (log-concentration) $P = 0.76$
				678.0	41/73	1.32 (0.71–2.43)	
				945.4	30/72	1.02 (0.53–1.95)	
			PCB-118	42.9	49	1.39 (0.78–2.47)	Continuous (log-concentration) $P = 0.42$
				61.0	31	0.89 (0.48–1.64)	
				104.7	27	0.81 (0.42–1.56)	
			PCB-138	53.2	39	1.33 (0.73–2.40)	Continuous (log-concentration) $P = 0.59$
				75.7	48	1.61 (0.89–2.92)	
				113.3	27	0.95 (0.49–1.83)	
			PCB-153	91.2	33	0.85 (0.47–1.54)	Continuous (log-concentration) $P = 0.55$
				120.3	45	1.38 (0.76–2.51)	
				170.0	30	0.82 (0.43–1.56)	
			PCB-180	63.4	33	1.02 (0.54–1.93)	Continuous (log-concentration) $P = 0.82$
				80.5	44	1.24 (0.66–2.31)	
				109.4	32	1.03 (0.52–2.02)	
			Immunotoxic congeners[b]	111.5	56	1.83 (1.01–3.31)	Continuous (log-concentration) $P = 0.48$
				149.6	30	0.94 (0.51–1.76)	
				228.7	25	0.89 (0.45–1.77)	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bertrand *et al.* (2010) USA (Physicians' Health Study cohort) 1982–2003	14 916 men; 205 cases and 409 controls	Serum, GC/ECD, lipid-corrected concentrations		Quintiles of PCB concentration (ng/g lipid)			Age, race, time and fasting status at blood draw (matching), region, height, BMI, alcohol, smoking 51 congeners measured[c]
			Total PCB	163–617	33	1.0	Continuous (log-concentration) $P < 0.01$
				> 617–742	31	0.86 (0.47–1.6)	
				> 742–894	34	0.99 (0.55–1.8)	
				> 894–1121	46	1.3 (0.71–2.3)	
				> 1121–5322	61	1.6 (0.91–2.9)	
			PCB-118	> 42–56	29	0.80 (0.42–1.5)	Continuous (log-concentration) $P = 0.15$
				> 56–77	40	1.1 (0.59–2.0)	
				> 77–105	46	1.2 (0.63–2.2)	
				> 105–734	57	1.4 (0.76–2.5)	
			PCB-138	> 59–76	38	1.3 (0.68–2.3)	Continuous (log-concentration) $P = 0.02$
				> 76–97	38	1.2 (0.64–2.1)	
				> 97–122	37	1.2 (0.64–2.2)	
				> 122–541	63	1.8 (0.98–3.2)	
			PCB-153	> 95–122	37	1.2 (0.67–2.3)	Continuous (log-concentration) $P < 0.01$
				> 121–148	36	1.3 (0.68–2.4)	
				> 148–188	37	1.2 (0.62–2.2)	
				> 188–761	67	2.1 (1.1–3.8)	
			PCB-180	> 68–84	40	1.5 (0.82–2.7)	Continuous (log-concentration) $P < 0.01$
				> 84–102	35	1.4 (0.75–2.7)	
				> 102–126	44	1.8 (0.96–3.3)	
				> 126–528	61	2.4 (1.3–4.5)	
			Immunotoxic congeners[b]	> 113–145	35	0.98 (0.54–1.8)	Continuous (log-concentration) $P = 0.09$
				> 145–189	36	0.99 (0.55–1.8)	
				> 189–245	45	1.2 (0.64–2.1)	
				> 245–1813	57	1.4 (0.80–2.6)	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Northern Europe (Norway, Denmark)							
Engel *et al.* (2007) Norway (JANUS cohort) 1972–1978 until 1999	87 600; 190 case–control pairs	Serum, HRGC/ID-HRMS, lipid-corrected concentrations		Median of quartiles of PCB concentration (ng/g lipid)			Age, sex, county, date of examination (matching), BMI, smoking status All cases ≥ 2 years from blood collection to diagnosis; 36 congeners measured[d]
			Total PCB	1398.3	48	1.1 (0.7–2.0)	
				1674.9	38	1.0 (0.5–1.9)	
				2148.2	60	1.7 (0.8–3.4)	*P* for trend < 0.05
			PCB-118	80.6	43	1.0 (0.5–2.0)	
				100.0	47	1.2 (0.6–2.3)	
				138.7	58	1.7 (0.9–3.5)	*P* for trend < 0.05
			PCB-138	122.8	29	0.6 (0.3–1.2)	
				153.4	42	0.9 (0.5–1.7)	
				190.0	68	1.7 (0.8–3.2)	*P* for trend < 0.05
			PCB-153	268.1	44	1.2 (0.6–2.3)	
				330.2	43	1.2 (0.7–2.2)	
				417.3	63	2.0 (1.0–3.9)	*P* for trend < 0.05
Bräuner *et al.* (2012) Copenhagen and Aarhus, Denmark (DCH cohort) 1994–97 until 2008	57 053; 239 cases and 245 controls	Adipose tissue, GC/MS, lipid-corrected concentrations		Quintiles of PCB concentration (ng/g lipid)		*IRR (95% CI)*	Age, sex (stratified), adjusted for BMI Lipid content by gravimetric method; 10 PCB congeners measured.[e] Participants with PCB concentrations < LOD were excluded from the analysis Case-content analysis
			Total PCB	770–939	55	0.74 (0.44–1.24)	
				939–1143	57	0.81 (0.48–1.35)	
				1143–1351	42	1.15 (0.63–2.11)	
				1351–2157	23	0.71 (0.34–1.45)	
				Linear estimate per IQR	239	0.99 (0.79–1.25)	
			PCB-118	25–34	63	0.88 (0.50–1.56)	
				34–48	58	0.96 (0.55–1.65)	
				48–62	34	0.67 (0.34–1.31)	
				62–150	25	0.72 (0.36–1.44)	
				Linear estimate per IQR	233	0.88 (0.68–1.14	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bräuner et al. (2012) Copenhagen and Aarhus, Denmark (DCH cohort) 1994–97 until 2008 (cont.)			PCB-156	28–34	51	0.59 (0.34–1.02)	
				34–41	54	0.68 (0.40–1.16)	
				41–50	45	0.94 (0.51–1.75)	
				50–88	23	0.66 (0.31–1.37)	
				Linear estimate per IQR	171	1.01 (0.79–1.29)	
			PCB-99	20–27	42	1.60 (0.85–3.01)	
				27–37	53	1.56 (0.84–2.89)	
				37–47	24	1.20 (0.58–2.49)	
				47–110	20	1.42 (0.59–3.40)	
				Linear estimate per IQR	171	1.09 (0.83–1.43)	
			PCB-138	100–140	44	0.66 (0.38–1.14)	
				140–180	74	1.04 (0.62–1.74)	
				180–230	41	1.25 (0.67–2.33)	
				230–380	26	0.68 (0.34–1.36)	
				Linear estimate per IQR	238	0.99 (0.78–1.26)	
			PCB-153	240–300	57	0.88 (0.52–1.50)	
				300–370	56	0.67 (0.40–1.12)	
				370–430	42	1.50 (0.81–2.78)	
				430–730	28	0.85 (0.42–1.73)	
				Linear estimate per IQR	239	0.97 (0.77–1.23)	
			PCB-170	87–100	47	1.19 (0.68–2.09)	
				100–130	69	0.93 (0.54–1.59)	
				130–150	42	1.46 (0.75–2.83)	
				150–230	23	0.80 (0.38–1.69)	
				Linear estimate per IQR	238	0.98 (0.72–1.33)	
			PCB-180	170–200	55	1.03 (0.60–1.77)	
				200–240	61	1.19 (0.69–2.05)	
				240–290	49	1.09 (0.59–2.01)	
				290–480	21	0.69 (0.32–1.46)	
				Linear estimate per IQR	239	0.99 (0.77–1.27)	

Table 2.7 (continued)

Reference, location follow-up period	Total subjects	Exposure assessment	Subgroup analysis	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Bräuner et al. (2012) Copenhagen and Aarhus, Denmark (DCH cohort) 1994–97 until 2008 (cont.)			PCB-183	19–24	35	0.58 (0.32–1.03)	
				24–31	69	0.91 (0.54–1.51)	
				31–39	40	1.03 (0.56–1.90)	
				39–65	23	0.68 (0.34–1.37)	
				Linear estimate per IQR	226	0.88 (0.70–1.10)	
			PCB-187	17–46	61	1.00	
				46–56	49	0.69 (0.40–1.17)	
				56–68	62	0.97 (0.57–1.64)	
				68–84	44	1.30 (0.68–2.47)	
				84–140	22	0.69 (0.33–1.44)	
				Linear estimate per IQR	238	0.92 (0.73–1.15)	
			PCB-201	6–15	43	1.00	
				15–19	62	0.98 (0.56–1.73)	
				19–23	58	1.20 (0.66–2.21)	
				23–28	36	0.82 (0.41–1.67)	
				28–45	25	0.88 (0.38–2.03)	
				Linear estimate per IQR	224	0.93 (0.68–1.28)	

[a] Congeners measured: PCBs 28, 52, 56, 74, 99, 101, 105, 110, 118, 138, 146, 153, 156, 170, 172, 177, 178, 180, 183, 187, 189, 193, 194, 195, 201, 203, and 206

[b] Immunotoxic congeners: PCB-66, PCB-74, PCB-105, PCB-118, PCB-156, and PCB-167

[c] Ninety-nine percent of samples had concentrations greater than the limit of detection for PCB congeners 74, 118, 138, 146, 153, 156, 170, 180, 187, 194, 196, 199, 203, 206, and 209

[d] Congeners measured: PCBs 126, 169, 74, 99, 118, 105, 146, 153, 138, 158, 167, 156, 157, 178, 187, 183, 177, 172, 180, 170, 189, 201, 196, 203, 195, 194, 206, 209; 26 with > 90% samples having concentrations greater than the limit of detection

[e] Congeners measured: PCBs 99, 118, 138, 153, 156, 170, 180, 183, 187, and 201. LOD, 0.10–1.00 ng/g lipid; proportion of subjects with values greater than the limit of detection ranged from 72% (PCB-99) to 100% (PCB-153 and PCB-180)

BMI, body mass index; ECD, electron capture detection; ER, estrogen receptor; FTP, full-term pregnancy; GC, gas chromatography; HRGC, high-resolution gas chromatography; ID-HRMS, isotope dilution high-resolution mass spectrometry; IRR, incidence rate ratio; IQR, interquartile range; LOD, limit of detection; mo, month; NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl

(sum of 51 congeners measured as lipid-corrected concentrations) or for specific congeners (PCB-118, PCB-138, PCB-153, PCB-180) after adjustment for several confounders. The same pattern of no association was observed in the subgroup analysis by the main subtypes of NHL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukaemia/small lymphocytic lymphoma. [This was the only nested case–control study on non-Hodgkin lymphoma to include women only. The Working Group noted that it was a well-designed study. The positive association observed in the initial study was not confirmed in the second, larger study, after adjustment for additional relevant confounders. However, in the second study the time since blood draw was prolonged and different laboratories and laboratory methods were used for analysis.]

The Physicians' Health Study began in 1982 in the USA as a randomized trial for the primary prevention of cardiovascular disease and cancer in male physicians aged 40–84 years at enrolment. A total of 14 916 participants provided a blood sample in 1982–84 (before randomization) and were followed until 2003 using annual questionnaires confirmed by review of medical records to identify newly diagnosed NHL (Bertrand *et al.*, 2010). After excluding those with a diagnosis within 6 months after blood collection, prior diagnosis of cancer, NHL of uncommon subtypes (i.e. mantle cell lymphoma), or lacking sufficient information for subtype classification, 205 cases with available blood samples were included. For each case, two subjects who were at risk of NHL when the case occurred were randomly selected as controls matched by race, age, and date of blood collection. Lipid-corrected concentrations of 51 PCB congeners in serum were determined for cases and controls. The odds ratio for the highest versus lowest quintile of total PCBs adjusted for matching variables was 1.9 (95% CI, 1.1–3.2), which was reduced to 1.6 (95% CI, 0.91–2.9) after adjustment for region, BMI, smoking status, alcohol intake, and height, in addition to matching variables. However, using the natural log of lipid-corrected concentrations of PCBs, the association was statistically significant for the fully adjusted model (P value < 0.01, OR not reported). The association was also significant for the log-concentrations of PCB-138, PCB-153 and PCB-180, as well as for the sum of PCBs -118, -138, -153 and -180. [The Working Group noted that this was a well-designed study with reasonable sample size. The multivariable adjustment weakened the association with total PCBs, but did not substantially change the interpretation.]

(ii) Northern Europe

Within the JANUS cohort, described in the previous section, 194 histologically confirmed cases of NHL were ascertained with follow-up to 1999 (median time to diagnosis, 16.6 years) (Engel *et al.*, 2007). Information, including lipid-corrected concentrations of 36 PCB congeners, was available for 190 case–control pairs matched by age, sex, county, and date of examination. In the analysis further adjustments were made for BMI and smoking status. The odds ratio for the association of NHL with the sum of PCBs was 1.7 (95% CI, 0.8–3.4) when comparing the fourth quartile with the first. A statistically significant increase in risk was reported for the highest to the lowest quartile of PCB-153 concentrations (OR, 2.0; 95% CI, 1.0–3.9), with a significant upward dose–response trend (P < 0.05). Odds ratios of 1.7 in the fourth exposure quartile and significant trends were also reported for PCB-118 and PCB-138. [The Working Group noted that the sample size, and therefore the power of the study, was in the range of that of the remaining nested case–control studies. It was not clear, therefore, why significant associations were found for three congeners, namely PCB-118, PCB-138, and PCB-153, but not for all PCBs combined.]

The association between NHL and PCB concentrations in adipose tissue was also studied among participants in the Danish diet and cancer

study (Raaschou-Nielsen *et al.*, 2005) described in section 2.2.3(a)(ii) (Bräuner *et al.*, 2012). Up to July 2008 (mean follow-up, 9.6 years), 278 initially cancer free cohort members were diagnosed with NHL; a subcohort of 256 participants was randomly selected for analysis using a case–cohort approach. Valid measurements of concentrations of 10 PCB congeners in adipose tissue were available for 239 cases and 245 subcohort members. Age was used as the timescale for the analysis, stratified by sex and adjusted for BMI. No association was observed between lipid-corrected concentrations of total PCBs in adipose tissue and risk of NHL. There was also no consistent association and no significant trend with PCB congeners. However, odds ratios were greater than 1 for all concentrations of PCB-99. [The Working Group noted that this was the largest nested case–control study on NHL and PCB concentrations measured in adipose tissue; estimates were adjusted only for age, sex, and BMI. The study explored the potential effect of all PCBs and a list of 10 specific congeners, with a consistent pattern of no association for all of them.]

(c) Cancer of the male genital tract

See Table 2.8

A nested case–control study on the risk of testicular germ cell tumours was carried out within the Norwegian JANUS cohort, described in Section 2.2.3(a)(ii) (Purdue *et al.*, 2009). Cases and controls were selected from cohort members with baseline blood collection without prior history of cancer. One male control was matched to each case by region, age group (2 years), and year of blood draw. Lipid-corrected measurements of the concentrations of 34 PCBs were available for 49 cases and 51 controls; 34 of the 49 cases were seminomas, 8 were non-seminomas, 5 were of mixed histology, and 2 were of unknown histology. There was no statistically significant association between risk of testicular germ cell tumours and total PCB concentration (OR, 1.3; 95% CI, 0.5–3.8 for the third versus the first quartile); however, there was an increased risk of testicular germ cell tumours for the highest versus the lowest tertile of PCB-99 concentration (OR, 2.2; 95% CI, 0.8–5.9) and of PCB-167 (OR, 4.4; 95% CI, 1.0–19.8). Cases of seminoma had significantly lower concentrations of congeners PCB-44, PCB-49, and PCB-52 and significantly higher concentrations of congeners PCB-99, PCB-138, PCB-153, PCB-167, PCB-183, and PCB-195. Similar patterns of elevated odds ratios were seen for PCB-99 and PCB-167 in this subgroup of cases. [The Working Group noted that this was a well-designed study, but with small sample size and very limited power.]

McGlynn *et al.* (2009) analysed concentrations of 15 PCBs in pre-diagnostic serum samples of 736 incident cases of testicular germ cell tumours and 913 controls matched to the cases on age, race, and serum draw date in a cohort of men in the United States military. The sum of PCB concentrations was significantly associated with decreased risk of all testicular germ cell tumours, and with non-seminoma and seminoma. Statistically significantly decreased risks of all testicular germ cell tumours were also associated with eight specific congeners (PCB-118, PCB-138, PCB-153, PCB-156, PCB-163, PCB-170, PCB-180, and PCB-187). Similar decreases in risk were observed for non-seminoma with the same congeners, while decreased risk of seminoma was associated with PCB-138, PCB-153, PCB-156, PCB-163, and PCB-170. Other congeners and groups of congeners were not associated with testicular germ cell tumours. In another study using data from 568 cases and 698 controls enrolled in the same cohort, Chia *et al.* (2010) examined associations between testicular germ cell tumours and 11 PCB congeners in relation to polymorphisms in hormone-metabolizing genes. A statistically significant reduced risk of testicular germ cell tumour for PCB-118 and PCB-138 was found only among subjects with the major homozygous allele for *HSD17B4*. [These appear

Table 2.8 Nested case-control studies on risk of cancer of the male genital tract and measured serum concentrations of PCBs

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Purdue *et al.* (2009) Norway (JANUS cohort) 1972–1978 until 1999	87 647 men; 49 cases and 51 controls	Serum, HRGC/ID-HRMS, lipid-corrected concentrations	TGC tumour (186)	Tertiles of PCB concentration			Age, county, period of blood draw (matching) 34 congeners measured
				Tertile 1	14	1.0	
				Tertile 2	16	1.1 (0.5–2.7)	
				Tertile 3	19	1.3 (0.5–3.8)	
				Selected PCB congeners: tertile 3, tertile 1 as referent:			
				PCB-44	18	0.6 (0.1–3.8)	
				PCB-49	20	1.2 (0.2–7.6)	
				PCB-52	20	1.0 (0.3–3.5)	
				PCB-99	21	2.2 (0.8–5.9)	
				PCB-138	24	1.8 (0.6–5.1)	
				PCB-153	19	1.2 (0.4–3.4)	
				PCB-167	19	4.4 (1.0–20.0)	
				PCB-183	18	1.3 (0.5–3.5)	
				PCB-195	15	1.7 (0.6–4.6)	
			Seminoma (n = 34)	Selected PCB congeners: tertile 3, tertile 1 as referent			
				PCB-44	12	0.2 (0.01–2.0)	
				PCB-49	14	0.3 (0.02–4.7)	
				PCB-52	14	0.4 (0.07–2.3)	
				PCB-99	17	4.4 (1.0–21)	
				PCB-138	17	2.1 (0.6–7.2)	
				PCB-153	13	1.2 (0.4–4.3)	
				PCB-167	15	6.7 (1.1–43)	
				PCB-183	14	2.9 (0.6–14)	
				PCB-195	13	3.0 (0.8–12)	
				Total PCBs	14	1.2 (0.4–4.1)	

Table 2.8 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
McGlynn *et al.* (2009), USA (STEED Study) 2002–2005	Military men [number not reported]; 736 cases and 913 controls	Blood, GC-MS lipid-adjusted concentrations; questionnaire	TGC tumours	Quartiles of PCB concentration (ng/g lipid)			Age, race/ethnicity, date of serum sample collection, serum DDE level, age at serum draw, BMI, height Quartile 1 as reference
				Total PCBs			
			TGC tumours	(158–250)	171	0.88 (0.67–1.16)	*P* for trend = 0.006
				(251–390)	175	0.73 (0.54 –0.98)	
				(> 390)	162	0.61 (0.43–0.86)	
			Seminoma	(158–250)	60	0.90 (0.6–1.35)	*P* for trend = 0.05
				(251–390)	91	0.89 (0.59–1.34)	
				(> 390)	88	0.64 (0.41–1.02)	
			Non-seminoma	(158–250)	111	0.84 (0.61–1.15)	*P* for trend = 0.007
				(251–390)	84	0.62 (0.43–0.88)	
				(> 390)	73	0.55 (0.37–0.83)	
				PCB-118			
			All TGC tumours	(7.2–10.5)	171	0.71 (0.53–0.94)	
				(10.6–15.6)	151	0.60 (0.45–0.81)	
				(> 15.6)	148	0.55 (0.40–0.76)	*P* for trend = 0.0007
				PCB-138			
				(15.6–24.5)	168	0.65 (0.48–0.88)	
				(24.6–37.7)	162	0.54 (0.39–0.75)	
				(> 37.7)	164	0.46 (0.32–0.66)	*P* for trend = 0.0001
				PCB-153			
				(23.4–37.2)	158	0.61 (0.45–0.82)	
				(37.3–56.3)	166	0.53 (0.38–0.73)	
				(> 56.3)	169	0.45 (0.31–0.66)	*P* for trend = 0.0003
				PCB-156			
				(5.3–6.9)	98	0.66 (0.48–0.90)	
				(7.0–10.0)	120	0.77 (0.56–1.06)	
				(> 10.0)	96	0.57 (0.40–0.81)	*P* for trend = 0.002

Table 2.8 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
McGlynn et al. (2009), USA (STEED Study) 2002–2005 (cont.)				*PCB-163*			
				(5.9–8.1)	128	0.70 (0.52–0.93)	
				(8.2–11.5)	110	0.55 (0.40–0.76)	
				(> 115)	131	0.59 (0.42–0.83)	*P* for trend = 0.001
				PCB-170			
				(6.5–9.7)	145	0.73 (0.55–0.98)	
				(9.8–14.5)	136	0.61 (0.44–0.84)	
				(> 14.5)	144	0.56 (0.39–0.80)	*P* for trend = 0.002
				PCB-180			
				(15.8–25.9)	177	0.83 (0.62–1.12)	
				(26.0–41.8)	176	0.68 (0.49–0.95)	
				(> 41.8)	161	0.56 (0.38–0.82)	*P* for trend = 0.003
				PCB-187			
				(5.8–8.0)	133	0.70 (0.52–0.94)	
				(8.1–11.6)	120	0.58 (0.42–0.81)	
				(> 11.6)	133	0.60 (0.42–0.86)	*P* for trend = 0.004
Chia *et al.* (2010) USA 2002–2005	568 cases and 698 controls	Blood, GC-MS lipid-adjusted concentrations; questionnaire	TGC tumours (186)	*PCB-118*			Age, race, date of serum sample, cryptorchidism, family history of testicular cancer, BMI
				AA genotype			Same cohort studied by McGlynn *et al.* (2009)
				(7.01–10.40)	100	0.66 (0.46–0.96)	AA genotype: AA-homozygous major allele *HSD17B4;* AA/TT genotype: minor allele for *HSD17B4*
							Quartile 1 as reference
				(10.41–15.56)	92	0.59 (0.40–0.87)	
				(> 15.57)	74	0.46 (0.31–0.70)	*P* for trend ≤ 0.001
				AT/TT genotype			
				(7.01–10.40)	38	1.27 (0.66–2.41)	
				(10.41–15.56)	31	1.06 (0.54–2.08)	
				(> 15.57)	43	1.69 (0.85–3.38)	*P* for trend = 0.019

Table 2.8 (continued)

Reference, location, follow-up period	Total subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Chia et al. (2010) USA 2002–2005 (cont.)				*PCB-138*			
				AA genotype			
				(15.85–25.00)	95	0.72 (0.49–1.07)	
				(25.01–38.53)	96	0.57 (0.38–0.85)	
				(> 38.53)	79	0.46 (0.30–0.72)	*P* for trend < 0.001
				AA/TT genotype			
				(15.85–25.00)	27	0.61 (0.31–1.20)	
				(25.01–38.53)	36	1.10 (0.54–2.25)	
				(> 38.53)	43	1.61 (0.76–3.41)	*P* for trend = 0.287
Sawada *et al.* (2010) 10 areas of Japan 1990–1995 until 2005	14 203 men; 201 cases and 402 controls	Serum, HRGC/ID-HRMS; lipid-corrected concentrations	Prostate	Quartiles of PCB concentration (ng/g lipid)			Age, area, date, and fasting hours at blood draw (matching), BMI, smoking, alcohol, marital status, intake of green tea and miso soup Sum of 41 congeners; LOD, 2 pg/g wet weight
				319–447	49	1.06 (0.63–1.79)	
				448–668	41	0.84 (0.49–1.46)	
				≥ 669	44	0.97 (0.51–1.87)	
						P for trend = 0.9	

BMI, body mass index; DDE, dichlorodiphenyldichloroethylene; ECD, electron capture detection; GC, gas chromatography; HRGC, high-resolution gas chromatography; ID-HRMS, isotope dilution high-resolution mass spectrometry; IRR, incidence rate ratio; LOD, limit of detection; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; STEED, US Servicemen's Testicular Tumor Environmental and Endocrine Determinants Study; TGC, testicular germ cell

to have been large, well-designed and well-implemented studies, but the consistent inverse associations of cancer risk with exposure to PCBs could not be explained biologically.]

The Japan Public Health Center-based Prospective Study was initiated in 1990. After excluding subjects from Tokyo for whom cancer information was not available, the cohort consisted of 65 657 men, of whom 14 203 (28%) donated blood between 1990 and 1995 (Sawada *et al.*, 2010). Up to December 2005, 201 newly diagnosed cases of cancer of the prostate were identified using several information sources (97% pathologically confirmed). For each case, two controls were selected from among subjects with no history of cancer of the prostate when the case was diagnosed, matched by age (within 3 years), public health-centre area, residence, date and time of day of blood collection, and duration of fasting. Lipid-corrected plasma concentrations of 41 PCB congeners were measured. Apart from matching variables, comparisons between cases and controls were further adjusted for BMI, smoking, alcohol, marital status, and intakes of green tea and miso soup. No statistically significant association with all cancers of the prostate was seen for total PCBs, for individual PCBs, or for PCBs grouped according to Wolff *et al.* (1997). No statistically significant differences were found for total PCBs according to stage (localized or advanced) at diagnosis of cancer of the prostate. [The Working Group noted that this was a well-designed and -conducted study showing null results; although the sample size was limited, power was reasonable for the main analysis, but limited for subgroup analyses.]

2.3 Case–control studies of occupational and environmental exposure

2.3.1 NHL

See Table 2.9

In a case–control study in Australia (Fritschi *et al.*, 2005), including 694 histologically confirmed cases of NHL, and 694 controls, exposure to PCBs was coded by an expert industrial hygienist based on questionnaire information. After adjusting by age, sex, residence and ethnicity, ever exposure to PCBs was not notably related to increased risk of NHL (OR, 1.10; 95% CI, 0.49–2.44) or to the subgroup of B-cell NHL (OR, 1.18; 95% CI, 0.53–2.62); however, risk was elevated among the subjects probably exposed (OR, 4.54; 95% CI, 0.97–21). Indicators of frequency, intensity, and duration of exposure did not show clear trends in risk. Occupational exposure to PCBs was very rare in this study, with only 25 subjects (13 cases and 12 controls) possibly or probably exposed. [The Working Group noted that this general-population case–control study may have been underpowered to detect associations with PCBs, given the low prevalence of exposure.]

A case–control study was conducted in an area of northern Italy where environmental exposure had resulted from soil contamination, most likely generated by spills from an adjacent factory producing PCBs and organochlorine chemicals. PCB concentration in the soil was used to define four areas with increasing concentrations of exposure. Overall, 495 cases of NHL, including 208 prevalent cases and 287 incident cases, identified in the Cancer Registry of the Brescia Local Health Authority, and 1467 population controls, randomly selected from the resident population, frequency-matched to cases by age and sex, participated in the study. Exposure to PCBs was assigned according to residence in one of three contaminated zones or a control zone, using three metrics: main lifetime residence; residence for at least 10 years in a given area; and duration of residence. Risk of NHL was elevated for subjects having resided 10 or more years in any of the three contaminated areas (OR, 1.4; 95% CI, 1.1–1.8), and particularly in the most polluted (OR, 1.9; 95% CI, 0.9–3.9).

Table 2.9 Case–control studies on risk of non-Hodgkin lymphoma and exposure to PCBs

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Fritschi *et al.* (2005), Australia 2000–01	694 694	Population	NHL (200, 202)	Retrospective expert assessment of occupational exposure to PCBs	Unexposed	681	1.0	Age, sex, state of residence, ethnicity
					Any exposure	13	1.10 (0.12–1.31)	
					Possible exposure	NR	0.40 (0.12–1.31)	
					Probable exposure	NR	4.54 (0.97–21)	
					Low intensity level	NR	1.91 (0.75–4.85)	
					Medium intensity level	NR	0.78 (0.17–3.50)	
					Intensity level			
					≤ 4 days/yr	NR	1.44 (0.49–4.22)	
					> 4 days/yr	NR	1.15 (0.35–3.81)	
					< 5 yr duration	NR	1.04 (0.26–4.19)	
					> 5 yr duration	NR	1.13 (0.43–2.97)	
Maifredi *et al.* (2011), Italy	495 1467	Population	NHL (200, 202)	Residence in PCB contaminated areas in Brescia, Italy; median total PCB soil concentration, 0.55 mg/kg	*Residence 1–9* yr			Age, sex Subjects who changed area of residence were repeatedly considered in each area; substantial overlapping in contamination among the areas; incident and deceased cases were included
					Most polluted area	13	1.4 (0.7–2.8)	
					All contaminated areas	21	0.8 (0.5–1.3)	
					Residence ≥ 10 yr			
					Most polluted area	15	1.8 (0.9–3.9)	
					All contaminated areas	80	1.4 (1.1–1.8)	
					Residence 10–19 yr			
					Most polluted area	10	3.8 (1.5–9.8)	
					All contaminated areas	25	1.7 (1.0–2.8)	
					Residence ≥ 20 yr			
					Most polluted area	5	0.8 (0.3–2.3)	
					All contaminated areas	55	1.3 (0.9–1.8)	
Hardell *et al.* (1996, 1997), Sweden	27 17	Hospital	NHL, B-cell type	Total PCBs in adipose tissue	≤ 1300 ng/g lipid		1.0	Age, sex
					> 1300 ng/g lipid		1.8 (0.4–7.4)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Hardell *et al.* (2001), Sweden	82 83	Hospital	NHL (200, 202)	PCBs in adipose tissue or lipid-adjusted serum				Age, sex, BMI, sample (blood or adipose tissue)
				Total PCBs	> 1020 ng/g lipid	51	1.8 (0.9–3.9)	Interaction with EBV-EA immunity assessed; pooled analysis of studies conducted at different times with different specimens 36 congeners measured
				Immunotoxic PCBs	> 1020 ng/g lipid	57	3.2 (1.4–7.4)	
				Total PCBs, EBV EA ≤ 80	> 1018 ng/g lipid	17	1.6 (0.5–5.1)	
				Total PCBs, EBV EA > 80	> 1018 ng/g lipid	22	4.0 (1.2–14)	
				Immunotoxic PCBs, EBV EA ≤ 80	> 348 ng/g lipid	18	3.2 (1.7–11)	
				Immunotoxic PCBs, EBV EA > 80	> 348 ng/g lipid	25	6.4 (1.9–24)	
Hardell *et al.* (2009), Sweden	99 99	Population	NHL (200, 202)	Lipid-adjusted plasma PCB concentrations				Age, sex, BMI, time of sampling
				Total PCBs	> Median	59	2.0 (0.99–3.9)	Both sexes; interaction with EBV-EA immunity assessed.
				Moderately chlorinated		58	1.8 (0.9–3.6)	
				Higher-chlorinated		63	1.7 (0.8–3.4)	
				Immunotoxic		54	1.5 (0.8–3.0)	
			Follicular lymphoma	Total PCBs	> 646 ng/g lipid	15	5.9 (1.9–14)	
				Immunotoxic	> 226 ng/g lipid	13	3.0 (0.9–11)	
			Diffuse large B-cell lymphoma	Total PCBs	> 646 ng/g lipid	19	1.6 (0.6–4.0)	
				Immunotoxic	> 226 ng/g lipid	19	1.4 (0.6–3.3)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Nordström *et al.* (2000), Sweden	54 54	Population	Hairy cell leukaemia	Lipid-adjusted serum PCB concentrations, EBV EA antibody titre				Age, BMI Only men; OR for total PCB
				Total PCBs	> 831.6 ng/g lipid; EBV EA > 40	13	4.4 (1.2–18.5)	> 831.6 ng/g lipid = 0.8 (0.3–1.9)
				Immunotoxic PCBs	> 285.4 ng/g lipid; EBV EA > 40	15	11.3 (2.3–73.1)	
Spinelli *et al.* (2007), Canada	422 460	Population	NHL (200, 202)	Lipid-adjusted plasma PCB concentration	Quartiles of exposure (ng/g lipid)			Age, sex, region, ethnicity, education, family history of NHL, BMI and farming; sum of 14 congeners
				Sum of PCBs	101–155.6	103	1.41 (0.93–2.14)	
					155.7–220.0	77	1.11 (0.71–1.74)	
					> 220.0	142	2.14 (1.38–3.30)	*P* for trend < 0.001
				DL-PCBs (105, 118, 156)	10.13–15.35	96	1.41 (0.91–2.16)	
					15.36–23.72	82	1.57 (1.00–2.46)	
					> 23.72	143	2.40 (1.53–3.77)	*P* for trend < 0.001
				PCB-105	> 1.32	132	1.06 (0.93–1.42)	
				PCB-118	4.58–7.78	88	1.12 (0.74–1.69)	
					7.79–12.85	95	1.23 (0.81–1.88)	
					> 12.85	129	1.77 (1.15–2.72)	*P* for trend = 0.004
				PCB-156	3.66–5.51	85	1.10 (0.72–1.68)	
					5.52–8.32	105	1.43 (0.93–2.21)	
					> 8.32	128	1.77 (1.14–2.74)	*P* for trend = 0.004
				NDL-PCBs (28, 99 138, 153, 180, 183, 187)	88.58–136.2	96	1.30 (0.85–1.97)	
					136.21–196.4	93	1.19 (0.76–1.86)	
					> 196.4	148	2.18 (1.41–3.38)	*P* for trend < 0.001
				PCB-28	Undetected	348	1.0 (Ref)	
					> 1.38	74	0.95 (0.67–1.34)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Spinelli et al. (2007), Canada (cont.)				PCB-99	3.07–4.83	82	0.78 (0.52–1.15)	
					4.84–7.78	85	0.81 (0.54–1.21)	
					> 7.78	130	1.27 (0.86–1.87)	*P* for trend = 0.045
				PCB-138	11.62–19.28	90	0.93 (0.62–1.38)	
					19.29–29.72	94	0.99 (0.66–1.50)	
					> 29.72	138	1.46 (0.98–2.18)	*P* for trend = 0.02
				PCB-153	25.3–38.68	86	1.04 (0.68–1.57)	
					38.69–59.0	106	1.34 (0.87–2.04)	
					> 59.0	140	1.79 (1.17–2.72)	*P* for trend = 0.002
				PCB-170	7.17–11.17	93	1.17 (0.77–1.79)	
					11.18–17.23	107	1.41 (0.91–2.18)	
					> 17.24	134	1.80 (1.16–2.79)	*P* for trend = 0.005
				PCB-180	21.94–35.63	94	1.28 (0.82–2.00)	
					35.64–54.72	89	1.25 (0.78–2.00)	
					> 54.72	126	1.91 (1.19–3.07)	*P* for trend = 0.005
				PCB-183	1.87–3.95	107	0.83 (0.59–1.18)	
					> 3.95	153	1.22 (0.87–1.71)	*P* for trend = 0.113
				PCB-187	5.94–9.82	98	1.27 (0.83–1.95)	
					9.83–15.46	79	1.04 (0.66–1.63)	
					> 15.46	136	1.92 (1.23–2.98)	*P* for trend = 0.003
			Follicular lymphoma	Total PCBs	Largest vs smallest quartile		2.0 (1.1–3.7)	
				DL-PCBs			2.5 (1.3–4.7)	
				PCB-105			0.9 (0.6–1.4)	
				PCB-118			2.0 (1.1–3.7)	
				PCB-156			2.4 (1.2–4.5)	
				NDL-PCBs			2.1 (1.1–3.9)	
				PCB-28			0.7 (0.4–1.3)	
				PCB-99			1.3 (0.8–2.3)	
				PCB-138			1.5 (0.9–2.7)	
				PCB-153			2.0 (1.1–3.7)	
				PCB-170			1.5 (0.8–2.8)	
				PCB-180			1.6 (0.8–3.1)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Spinelli et al. (2007), Canada (cont.)			Diffuse large B-cell lymphoma	PCB-183			1.6 (1.0–2.7)	
				PCB-187			1.8 (1.0–3.3)	
				Total PCBs	Largest vs smallest quartile		1.8 (0.8–4.1)	
				DL-PCBs			2.1 (0.9–4.9)	
				PCB-105			0.8 (0.5–1.5)	
				PCB-118			2.0 (0.9–4.7)	
				PCB-156			1.3 (0.6–3.0)	
				NDL-PCBs			1.8 (0.8–4.1)	
				PCB-28			1.3 (0.7–2.4)	
				PCB-99			1.0 (0.5–2.0)	
				PCB-138			1.2 (0.6–2.6)	
				PCB-153			1.3 (0.6–2.7)	
				PCB-170			1.6 (0.7–3.6)	
				PCB-180			1.2 (0.5–2.9)	
				PCB-183			0.8 (0.4–1.6)	
				PCB-187			1.7 (0.7–4.0)	
Cocco *et al.* (2008), France, Spain, Germany	174 203	Hospital and population	NHL (200, 202)	Lipid-adjusted plasma PCB concentration (ng/g lipid) Total PCBs	200.43–387.79	50	1.2 (0.6–2.2)	Age, sex, education, centre Sum of 9 congeners LOD, 0.20–0.50 µg/L
					387.8–576.36	33	0.7 (0.3–1.4)	
					> 576.36	50	1.0 (0.5–2.0)	*P* for trend = 0.83
				PCB-28	10.51–31.70	25	0.9 (0.4–1.8)	
					31.71–67.94	21	0.7 (0.3–1.5)	
					> 67.94	45	1.6 (0.8–3.2)	*P* for trend = 0.23
				PCB-118	12.31–38.76	41	1.0 (0.5–2.0)	
					38.77–59.17	20	0.5 (0.2–2.0)	
					> 59.18	19	0.4 (0.2–0.8)	*P* for trend = 0.004
				PCB-138	45.74–72.41	37	1.1 (0.6–1.9)	
					72.42–116.12	42	1.1 (0.6–2.0)	
					> 116.12	44	1.1 (0.6–2.0)	*P* for trend = 0.88

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cocco et al. (2008), France, Spain, Germany (cont.)				PCB-153	62.57–100.66	51	1.5 (0.8–2.8)	
					100.67–142.43	28	0.8 (0.4–1.6)	
					> 142.43	52	1.3 (0.7–2.5)	*P* for trend = 0.70
				PCB-170	0.21–21.53	40	1.1 (0.5–2.2)	
					21.54–34.28	36	0.8 (0.4–1.7)	
					> 34.28	45	1.0 (0.5–1.8)	*P* for trend = 0.83
				PCB-180	0.31–51.22	40	1.2 (0.6–2.6)	
					51.23–85.93	50	1.4 (0.6–3.0)	
					> 85.93	61	1.5 (0.7–3.2)	*P* for trend = 0.31
			Chronic lymphocytic leukaemia	Total PCBs	200.43–387.79	15	1.4 (0.5–4.4)	
					387.8–576.36	10	0.8 (0.2–2.8)	
					> 576.36	18	1.4 (0.4–4.5)	*P* for trend = 0.71
				Immunotoxic PCBs	> median	NR	3.2 (0.9–12)	Subgroup analysis of combined French and German subjects
			Diffuse large B-cell lymphoma	Total PCBs	200.43–387.79	12	0.8 (0.3–2.1)	
					387.8–576.36	7	0.5 (0.1–1.6)	
					> 576.36	13	0.9 (0.3–2.5)	
De Roos et al. (2005), USA	100 100	Population	NHL (200, 202)	Lipid-adjusted plasma PCB concentration (ng/g lipid)	Quartiles of PCB concentration			Sex, study site, birth date, and date of blood draw
				PCB-74	7.8–13.3	28	1.12 (0.51–2.45)	
					13.4–19.3	16	0.73 (0.30–1.75)	
					> 19.4	31	1.26 (0.52–3.03)	*P* for trend = 0.66
				PCB-99	5.6–9.3	22	0.63 (0.24–1.68)	
					9.4–16.1	30	1.04 (0.45–2.39)	
					> 16.1	24	0.77 (0.28–2.10)	*P* for trend = 1.0
				PCB-118	8.1–11.8	14	0.36 (0.13–0.98)	
					11.9–25.8	30	0.91 (0.42–1.98)	
					> 25.8	24	0.73 (0.29–1.84)	*P* for trend = 0.88

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
De Roos et al. (2005), USA (cont.)				PCB-138–158	25.2–38.3	20	0.82 (0.38–1.78)	
					38.4–55.5	25	1.04 (0.47–2.33)	
					> 55.5	29	1.42 (0.49–3.05)	*P* for trend = 0.53
				PCB-146	4.4–6.0	24	1.06 (0.36–3.08)	
					6.1–8.7	24	1.37 (0.50–3.79)	
					> 8.7	32	1.81 (0.70–4.64)	*P* for trend = 0.17
				PCB-153	37–56.2	27	1.36 (0.54–3.25)	
					56.3–71.3	16	0.80 (0.32–2.03)	
					> 71.3	34	1.59 (0.63–4.00)	*P* for trend = 0.40
				PCB 156	5.6–7.8	27	1.70 (0.48–6.03)	
					7.9–9.8	16	1.02 (0.32–3.26)	
					> 9.8	40	2.70 (0.97–7.50)	*P* for trend = 0.03
				PCB-170	12.2–17.0	16	0.84 (0.36–1.92)	
					17.1–22.5	27	1.59 (0.63–4.02)	
					> 22.5	31	1.73 (0.73–4.14)	*P* for trend = 0.13
				PCB-180	28.7–41.2	21	1.72 (0.65–4.54)	
					41.3–54.4	22	1.82 (0.70–4.76)	
					> 54.4	41	3.50 (1.53–9.15)	*P* for trend = 0.01
				PCB-183	2.8–4.4	21	0.93 (0.16–5.46)	
					4.5–6.3	22	0.73 (0.26–2.06)	
					> 6.3	27	1.02 (0.36–2.93)	*P* for trend = 0.96
				PCB-187	8.9–12.0	13	0.59 (0.22–1.57)	
					12.1–18.0	33	1.34 (0.59–3.04)	
					> 18.0	30	1.22 (0.49–3.08)	*P* for trend = 0.18
				PCB-194	8.0–11.2	24	1.59 (0.62–4.04)	
					11.3–15.6	20	1.35 (0.53–3.48)	
					> 15.6	37	2.68 (1.04–6.90)	*P* for trend = 0.04
				PCB-126 (pg/g lipid)	19.0–30.3	20	0.65 (0.29–1.49)	
					30.4–52.7	21	0.73 (0.31–1.72)	
					> 52.7	30	1.09 (0.49–2.41)	*P* for trend = 0.54

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
De Roos et al. (2005), USA (cont.)				PCB-169 (pg/g lipid)	18.6–28.4	23	1.14 (0.49–2.66)	
					28.5–37.7	20	1.08 (0.41–2.82)	
					> 37.7	35	2.62 (0.88–7.80)	*P* for trend = 0.11
				Lower chlorinated PCBs (2–4) (mmol/g lipid)	0.028–0.046	28	1.12 (0.51–2.45)	
					0.047–0.066	16	0.73 (0.30–1.75)	
					> 0.067	31	1.26 (0.52–3.03)	*P* for trend = 0.66
				Moderately chlorinated PCBs (5–7) (mmol/g lipid)	0.386–0.599	25	1.52 (0.58–4.01)	
					0.600–0.785	20	1.43 (0.49–4.11)	
					> 0.785	29	1.88 (0.67–5.26)	*P* for trend = 0.29
				Highly chlorinated PCBs (8–10) (mmol/g lipid)	0.019–0.026	24	1.59 (0.62–4.04)	
					0.027–0.036	20	1.35 (0.53–3.48)	
					> 0.036	37	2.68 (1.04–6.90)	*P* for trend = 0.04
				PCB TEQ (summed pg/g lipid, weighted by TEF)	6.41–8.69	16	0.59 (0.25–1.40)	
					8.70–13.17	20	0.86 (0.38–1.98)	
					> 13.17	33	1.51 (0.62–3.67)	*P* for trend = 0.06
Colt *et al.* (2009), USA	685 646	Population	NHL (ICDO-3)	PCB-180 in carpet dust			*Risk increase in % per 10% increase in concentration*	Age, sex, race, study centre, education
					IFNG (C–1615T) TT	243	1.2 (0.1–2.4)	
					IL4 (5′-UTR, Ex1-168C>T) CC	403	1.0 (0.1–1.9)	
					IL16 (3′-UTR, Ex22-871A>G) AA	330	1.1 (0.1–2.1)	
					IL8 (T–251A) TT	172	1.4 (0.05–2.8	
					IL10 (A–1082G) AG/GG	431	0.9 (0.05–1.8)	
	100 100	Population		PCB-180 in plasma	*IFNG* (C–1615T) TT	39	16.9 (3.7–31.6)	
					IL4 (5′-UTR, Ex1-168C>T) CC	62	9.3 (0.9–18.3)	
					IL16 (3′-UTR, Ex22-871A>G) AA	46	15 (3.2–28.0)	
					IL8 (T–251A) TT	27	28.9 (6.4–56.1)	
					IL10 (A–1082G) AG/GG	59	9.9 (1.2–19.4)	

Table 2.9 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Organ site (ICD code)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Colt et al. (2009), USA (cont.)				TEQ in plasma	*IFNG* (C–1615T) TT	39	19.2 (4.8–35.7)	
					IL4 (5′-UTR, Ex1-168C>T) CC	60	12.5 (3.0–22.9)	
					IL16 (3′-UTR, Ex22-871A>G) AA	44	11.2 (–0.3–24.0)	
					IL8 (T–251A) TT	61	9.1 (0.4–18.6)	
					IL10 (A–1082G) AG/GG	57	5.0 (–3.0–13.8)	
Wang *et al.* (2011), USA	685 646	Population	NHL (ICDO-3)	PCB-180 in carpet dust	> 20.7 ng/g HLA-DRB1*0101 absent	81	1.36 (0.93–1.99)	Age, sex, race, study centre
					> 20.7 ng/g HLA-DRB1*0101 present	17	1.25 (0.66–2.38)	No risk estimates presented for AH 8.1 present genotype. In analysis by major lymphoma subtypes, no increase in risk for DLBCL or follicular lymphoma
	100 100	Population		PCB-180 lipid-adjusted plasma concentration	> 28.7 ng/g lipid HLA-DRB1*0101 absent	65	3.93 (1.49–10.35)	
					> 28.7 ng/g lipid HLA-DRB1*0101 present	10	0.66 (0.18–2.37)	

BMI, body mass index; DLBCL, diffuse large B-cell lymphoma; DL-PCB, dioxin-like PCB; EA, early antigen; EBV, Epstein–Barr virus; Ex, exon; IFNG, inferon gamma; IL, interleukin; LOD, limit of detection; NA, not applicable; NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; ref, reference; NDL-PCB, non-dioxin-like PCB; TEF, toxic equivalency factor; TEQ, toxic equivalent; vs, versus

Risk was highest for those who had resided 10–19 years in the most polluted area (OR, 3.8; 95% CI, 1.5–9.8) (Maifredi *et al.*, 2011). [The authors used the ICD-9 classification to define NHL, and therefore did not include chronic lymphocytic leukaemia among their cases, which precluded any feasible analysis of specific NHL subtypes.]

Several small case–control studies in Sweden used adipose tissue or serum levels of total PCBs and individual congeners as the exposure indicator. In a first study with 27 cases and 17 controls (Hardell *et al.*, 1996, 1997), risk of NHL was elevated for total PCB concentrations [17 congeners] above the median among controls (OR, 1.8; 95% CI, 0.4–7.4), after adjusting for age and sex. Thirty-six PCB congeners were measured in a second study with 82 cases of NHL and 83 controls. The odds ratio was significantly increased for concentration of immunotoxic PCBs (Moysich *et al.*, 1999a) above the median among the controls (OR, 3.2; 95% 1.4–7.4) (Hardell *et al.*, 2001). An interaction was observed between elevated concentrations of total and immunotoxic PCBs above the median and EBV-EA antibodies: EBV-EA seropositivity (EBV-EA antibody titre >80) and adipose total PCB concentrations were associated with an increase in risk of NHL of two- to fourfold, which was highest when the immunotoxic PCB subgroup was considered (OR, 6.4; 95% CI, 1.9–24). When the low-grade B-cell NHLs were analysed separately, risk associated with elevated median concentrations of immunotoxic PCBs among subjects with EBV-EA seropositivity was increased 17-fold (95% CI, 3.1–150; 16 cases) (Hardell *et al.*, 2001).

Another case–control study in Sweden included 99 cases of NHL and 99 population controls, matched to cases by age, sex, and health-service region (Hardell *et al.*, 2009). After adjusting by age, sex, and BMI, risk of NHL was elevated for values above the median among controls for the sum of PCBs (OR, 2.0; 95% CI, 0.99–3.9), and to a lesser extent for the subgroups of moderately chlorinated PCBs, highly chlorinated PCBs, or immunotoxic PCBs. Risk was highest for follicular lymphoma for the subgroup of highly chlorinated PCBs (OR, 9.6; 95% CI, 1.9–49; 18 cases); immunotoxic PCBs (OR, 3.0; 95% CI, 0.9–11); and less chlorinated PCBs (OR, 2.8; 95% CI, 0.9–9.0). Risks were only moderately and non-significantly elevated for diffuse large B-cell lymphoma. When stratified by EBV-EA antibody titre, risk of NHL associated with total PCB concentration above the median was 5.2 (95% CI, 1.9–14) among EBV-EA-positive subjects, and ranged from 3.0 to 5.0 for the above-mentioned PCB subgroups; risk for diffuse large B-cell lymphoma ranged from 3.8 to 7.0 by PCB subgroup (all statistically significant), and was 6.2 (95% CI, 1.6–25) for immunotoxic PCBs (Hardell *et al.*, 2009).

A case–control study focused on 54 cases of hairy cell leukaemia [a rare subtype of NHL] identified in the Swedish Cancer registry, and 54 controls drawn from the national population registry, matched to cases by age, sex, and county (Nordström *et al.*, 2000). Concentrations of 36 PCBs were measured in plasma. Overall, risk was not elevated for total PCB concentration greater than the median value (OR, 0.8; 95% CI, 0.3–1.9). When stratifying by EBV-EA antibody titre, the odds ratio for exposure above the median of values was 4.4 (95% CI, 1.2–18.5; 13 cases) for total PCBs and 11.3 (95% CI, 2.3–73.1; 15 cases) for immunotoxic PCBs among subjects with EBV-EA titres ≥ 40 (Nordström *et al.*, 2000). [The Working Group highlighted some methodological concerns about this group of studies, including poor precision, recruitment of cases and controls at different times, some with PCB measurements in adipose tissue and others with measurements in plasma.]

The largest case–control study of PCB body burden in relation to risk of NHL was conducted in Canada (Spinelli *et al.*, 2007). Lipid-adjusted concentrations of 14 PCB congeners were measured in pretreatment samples of plasma from

422 cases of NHL and 460 population controls, frequency-matched to cases by 5-year age-groups, sex, and residence. Odds ratios were adjusted for age, sex, education, BMI, ethnicity, farming, and family history of NHL. Risk of NHL was found to be highest in the highest quartile of the sum of dioxin-like PCBs (OR, 2.40; 95% CI, 1.53–3.77) and of non-dioxin-like congeners (OR, 2.18; 95% CI, 1.41–3.38). Individual congeners showing a significant excess risk in the top quartile of plasma concentration included PCB-118 and PCB-156, among the dioxin-like PCBs, and PCB-138, PCB-153, PCB-170, PCB-180, and PCB-187, among the non-dioxin-like PCBs. The observed associations were consistent across the four NHL subtypes examined, including DLBCL, follicular lymphoma, T-cell lymphoma, and other B-cell lymphomas (Spinelli *et al.*, 2007). [This was one of the largest studies of NHL and PCBs, and accounted for relevant confounders. The Working Group judged it to be a high-quality study, which was notable for providing results for individual congeners and lymphoma subtypes. While the participation rate for controls was less than 50%, the Working Group noted that this was typical of the available case–control studies and that potential confounding factors, including education, were comparable between cases and controls despite differences in participation. The most consistent associations were seen for follicular lymphoma and exposure to dioxin-like PCBs.]

A multicentre European study of NHL included 174 cases and 203 controls from France, Germany, and Spain (Cocco *et al.*, 2008). Patients admitted to the same hospital as the cases for non-cancer diseases not related to known risk factors for NHL were selected as controls in France and Spain; controls in Germany were a random sample of the general population. Concentrations of nine PCB congeners were measured in plasma, and risk estimates were adjusted by age (continuous), sex, education, and centre. Risk of NHL did not increase by quartile of plasma concentration of total PCBs, or specific congeners, or the functional PCB congener groups as defined by Hansen (Hansen, 1998). When exploring risk by lymphoma subtype, a nonsignificant increase was observed for chronic lymphocytic leukaemia in the top quartile of concentration of immunotoxic PCBs and BRCA1-inhibiting PCBs, with no indication of an increasing trend, or of an association with specific PCB congeners. No association was observed with risk of diffuse large B-cell lymphoma. However, risk of chronic lymphocytic leukaemia associated with plasma concentrations of immunotoxic PCBs above the median showed a threefold increase (OR, 3.2; 95% CI, 0.9–11.5), increasing to sixfold (OR, 6.1; 95% CI, 1.0–37.8) in the upper quartile, in subgroup analyses of the German and French subgroups combined, but not in the Spanish subgroup; a significant heterogeneity by country was observed for risk of chronic lymphocytic leukaemia associated with immunotoxic PCBs, but not for the sum of total PCBs. [The Working Group judged this international study to be high in quality; the classification of lymphoma was particularly meticulous. Although the overall results were null, the association of immunotoxic PCBs with chronic lymphocytic leukaemia in two of the three centres is noteworthy. The heterogeneity between countries may have been a result of differences in PCB exposure or distribution of confounding factors.]

Pretreatment plasma samples were available in a subset of 100 cases with a histologically confirmed diagnosis of NHL and 100 controls out of the 1321 cases and 1057 general population controls who participated in a case–control study on NHL conducted by the United States National Cancer Institute in 1998–2000 in four areas with population-based cancer registries (Iowa, Los Angeles, CA, Detroit, MI, and Seattle, WA) (De Roos *et al.*, 2005). Concentrations of 36 non-coplanar and 4 coplanar congeners were measured in plasma. Risk of NHL overall and of its major subtypes was analysed in relation

to 28 PCB congeners detected in at least 30% of samples. Values below the detection limit were estimated by multiple imputation. Odds ratios were adjusted for the matching factors, age, sex, study site, and date of blood draw. Other potential confounders were tested, including education, race, BMI, and family history of NHL, but no confounding was observed. The results showed significant upward trends in risk of NHL with increasing quartiles of plasma concentration of the subgroup of highly chlorinated PCB congeners (test for trend, $P = 0.04$), which included PCB-156, PCB-180, and PCB-194. An increase of 10 TEQ pg/g lipid was associated with a 35% excess risk of NHL (95% CI, 1.02–1.79). Some associations were stronger among the 14 cases of DLBCL than the 25 cases of follicular lymphoma, both in men and women, and trends by exposure quartiles became significant for follicular lymphoma for PCB-180 and PCB-187 (De Roos *et al.*, 2005). [Despite the extensive analysis, this was a relatively small study, with wide confidence intervals.]

Colt *et al.* (2009) used the same data set to explore the interaction between common variants in genes implicated in the immune and inflammatory response and PCB-180, (the non-dioxin like PCB that showed the strongest association between NHL and levels measured in plasma (100 cases and 100 controls) and carpet dust (682 cases and 513 controls) in the analysis by De Roos *et al.* (2005). Sixty-one single nucleotide polymorphisms in 36 proinflammatory and other immunoregulatory genes were analysed in samples of blood or buccal cells. Relative risk estimates were adjusted for sex, age, race, education, and study centre. The concentration of PCB-180 in plasma was associated with increased risk of NHL (OR, 8.3%; 95% CI, 1.9–14.6% per 10% increment), but the concentration in carpet dust was not (OR, 0.7%; 95% CI, 0.0–1.3% per 10% increment). Significant increases in risk of NHL were observed for PCB-180 in both plasma and carpet dust and for *IFNG* (C–1615T) TT, *IL4* (5′-UTR, Ex1-168C>T) CC, *IL16* (3′-UTR, Ex22-871A>G) AA, *IL8* (T–251A) TT, and *IL10* (A–1082G) AG/GG genotypes (Colt *et al.*, 2009).

Another analysis was conducted on the same data set to explore the interaction between status of HLA-DRB1*01:01 class II leukocyte surface antigen and of the extended ancestral haplotype (AH) 8.1 (HLA-A*01-B*08-DR*03-TNF-308A) and blood concentrations of PCB-180 above the median in the control group. Risk of NHL overall was elevated among study subjects lacking the HLA-DRB1*01:01 allele or the AH 8.1 allele (OR, 3.93; 95% CI, 1.49–10.35). No significant increase in risk was observed with PCB-180 in carpet dust or for DLBCL or follicular lymphoma (Wang *et al.*, 2011). [These related studies were well conducted, but the subgroup analyses were based on small numbers.]

2.3.2 Cancer of the breast

See Table 2.10

(a) Smaller studies

Case–control studies of cancer of the breast with 100 or fewer cases, most published before 2000, are reviewed here briefly and are not presented in the table. Most of these studies did not present risk estimates according to PCB concentrations.

One of the earliest studies looked at PCB concentrations in samples of breast adipose tissue from 14 living and 18 deceased patients with cancer of the breast, 21 similar samples from non-cancer patients, and samples of adipose tissue from 35 non-cancer autopsies, and found no significant differences (Unger *et al.*, 1984).

In another study, mean concentrations of PCBs in the breast tissue of 20 women with cancer of the breast were significantly higher ($P = 0.02$) than in 20 women with benign breast disease, and the association persisted after controlling for age, smoking, and BMI (Falck *et al.*, 1992).

Table 2.10 Case-control studies on cancer of the breast and exposure to PCBs

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Recio-Vega *et al.* (2011), Comarca Lagunera, Mexico	70 70	Hospital-based: 70 women with biopsies negative for malignancy, from the same hospital	Questionnaire; serum concentrations of 20 PCB congeners[a] measured by GC	Total PCBs	NR	1.09 (1.02–1.16)	Age, age at menarche, lactation, menopausal status, BMI, family history of breast cancer [The Working Group was not clear on how analysis was performed to obtain risk estimates.] PCb groups according to Wolff & Toniolo (1995)
				Premenopausal	NR	1.08 (0.99–1.17)	
				Postmenopausal	NR	1.13 (1.01–1.25)	
				Group 1a	NR	1.19 (0.81–1.7)	
				Group 1b	NR	1.40 (0.94–2.1)	
				Group 2a	NR	1.22 (0.99–1.49)	
				Group 2b	NR	1.90 (1.25–2.88)	
				Group 3	NR	1.81 (1.08–3.04)	
				Group 4	NR	1.57 (1.20–2.07)	
				Group 5	NR	1.30 (0.84–2.04)	
Moysich *et al.* (1998, 1999b), Erie and Niagara counties of western New York, USA, 1986–1991	154 postmenopausal women with incident primary breast cancer identified from hospitals 192 controls	Community controls frequency matched by age and county of residence	Structured interview; *CYP1A1* polymorphism was determined by PCR-RFLP; Lipid-adjusted serum PCBs (56 congener peaks based on the concentrations of 73 congeners) measured by GC (ng/g lipid)	*Total PCBs:* PCB low (0.75–3.72 ng/g):			Age, education, family history of breast cancer, parity, quetelet index (BMI), duration of lactation, age at first birth, serum lipids, years since last pregnancy, fruit and vegetable intake, serum lipids, and smoking status
				Ile:Ile	62	1.00	
				Ile:Val/Val:Val	8	0.88 (0.29–2.70)	
				PCBs > 3.72 ng/g:			
				Ile:Ile	65	1.08 (0.62–1.89)	
				Ile:Val/Val:Val	19	2.93 (1.18–7.45)	
				Total PCBs: All subjects:			
				2.93–4.43	45	0.70 (0.37–1.29)	
				4.44–19.04	56	1.14 (0.61–2.15)	$P = 0.51$
				Never lactated ($n = 107$):			
				2.93–4.43	15	1.71 (0.55–5.35)	
				4.44–19.04	20	2.87 (1.01–7.29)	$P = 0.07$
				Ever lactated ($n = 191$):			
				2.93–4.43	41	0.38 (0.17–1.03)	
				4.44–19.04	36	0.71 (0.31–1.61)	$P = 0.72$
				Less chlorinated			Data NR for women who never lactated
				0.01–0.31	59	2.04 (1.09–3.83)	
				0.32–1.65	63	1.40 (0.76–2.59)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Moysich et al. (1998, 1999b), (cont.)				*Moderately chlorinated*			
				All subjects:			
				2.20–3.12	41	0.57 (0.03–1.07)	
				3.13–15.07	60	1.37 (0.73–2.59)	*P* = 0.69
				Never lactated:			
				2.20–3.12	12	0.73 (0.22–2.63)	
				3.13–15.07	23	3.57 (1.10–8.60)	P = 0.08
				Highly chlorinated			
				All subjects:			
				0.26–0.44	43	0.79 (0.42–1.52)	
				0.45–1.30	54	1.19 (0.60–2.36)	
				Never lactated:			
				0.26–0.44	11	0.51 (0.15–1.69)	
				0.45–1.30	21	1.53 (0.47–4.95)	
Wolff *et al.* (2000b), New York, New York, USA	175 cases with incident breast cancer 355 controls	Hospital controls matched by age, race/ethnicity	Structured interview in person or by telephone Lipid-adjusted serum PCB concentration (µg/g lipid)	Tertiles of PCB concentration (µg/g lipid)			Age, age^2, menopausal status, race, BMI, family history of breast cancer, lactation, parity Tumor stage and markers (ER, PR, p53, erbB-2) identified histologically and immunohistochemically by pathologist ORs not reported by tumour marker status
				Highly chlorinated			
				0.460–0.798	46	0.88 (0.52–1.5)	
				0.799–3.3	46	0.78 (0.45–1.3)	
				Less chlorinated			
				0.085–0.162	54	1.47 (0.84–2.6)	
				0.163–2.39	38	0.96 (0.53–1.7)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Millikan *et al.* (2000), North Carolina, USA 1993–1996	748 cases, aged 20–74 years 659 controls	Population-based, frequency-matched to cases on race and age	Structured interview. Lipid-adjusted plasma concentrations of PCBs measured by GC (μg/g lipid)	Tertiles of PCB concentration			Age, age^2, race (all participants), menopausal status, BMI, parity, lactation, use of HRT, and income Response rates: cases, 76%; controls, 55%. PCB and lipid measurements were available for 748 cases (84%) and 659 controls (78%)
				Total PCBs			
				All women:			
				0.283–0.468	266	1.29 (0.97–1.72)	
				≥ 0.469	243	1.09 (0.79–1.52)	
				African-American:			
				0.312–0.53	97	1.35 (0.84–2.16)	
				≥ 0.54	116	1.74 (1.00–3.01)	
				White:			
				0.265–0.416	172	1.32 (0.92–1.90)	
				≥ 0.417	135	1.03 (0.68–1.56)	
				Low to moderately chlorinated			
				Tertile 2	NR	0.96 (0.73–1.27)	
				Tertile 3	NR	0.99 (0.73–1.35)	
				Highly chlorinated			
				Tertile 2	NR	1.41 (1.05–1.87)	
				Tertile 3	NR	1.35 (0.97–1.88)	
Li *et al.* (2005), North Carolina, USA, 1993–1996 (same population as Millikan *et al.*, 2000)	612 cases 599 controls	Population	Lipid-adjusted plasma PCB concentration by GC (ng/g lipid)	*Total PCBs*		*CYP1A1 M1* genotype	Age, race, parity, use of HRT, oral-contraceptive use, breast feeding, smoking, alcohol consumption, income, education, height, waist/hip ratio, BMI See Millikan *et al.* (2000) for details
				African-American:			
				< 0.430	66	Non-M1: 1.0 (Ref)	
				≥ 0.430	75	Non-M1: 1.5 (0.9–2.5)	
				< 0.430	42	Any M1: 1.0 (0.6–1.7)	
				≥ 0.430	59	Any M1: 1.4 (0.8–2.5)	Interaction contrast ratio: 0.0 (–0.9–0.9)
				White:			
				< 0.349	174	Non-M1: 1.0 (Ref)	
				≥ 0.349	122	Non-M1: 0.7 (0.5–1.0)	
				< 0.349	45	Any M1: 0.8 (0.5–1.2)	
				≥ 0.349	29	Any M1: 0.8 (0.4–1.4)	Interaction contrast ratio: 0.4 (–0.2–0.9)

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Li et al. (2005), (cont.)							Likelihood ratio test for both groups not statistically significant
				White:		*CYP1A1 M2* genotype	
				< 0.349	210	Non-M2: 1.0 (Ref)	
				≥ 0.349	138	Non-M2: 0.7 (0.5–1.0)	
				< 0.349	11	Any-M2: 0.4 (0.2–0.8)	
				≥ 0.349	15	Any-M2: 0.9 (0.4–1.9)	Interaction contrast ratio: 0.8 (0.1–1.6)
							Likelihood ratio test: $P = 0.02$
				African-American:		*CYP1A1 M3* genotype	
				< 0.430	95	Non-M3: 1.0 (Ref)	
				≥ 0.430	105	Non-M3: 1.3 (0.8–2.0)	
				< 0.430	13	Any M3: 0.6 (0.3–1.2)	
				≥ 0.430	29	Any M3: 1.6 (0.8–3.2)	Interaction contrast ratio: 0.8 (–0.3–1.9)
							Likelihood ratio test: $P = 0.10$
Demers *et al.* (2000, 2002), Quebec City, Quebec, Canada, 1994–1997	315 women with histologically confirmed infiltrating primary breast cancer 523 controls	Hospital and population, 523 cases frequency-matched by age and rural/urban residence	Telephone interview. Lipid-adjusted serum concentrations for 14 PCB congeners[b] measured by GC/ECD (μg/g lipid)	Quartiles of PCB concentration			Age, region of residence, BMI, history of benign breast disease, breastfeeding duration Participation rate: cases, 91%; hospital controls, 89%; and population controls, 47%. PCBs 28, 52, 101, 105 and 128 were detected in < 70% of women and were excluded from analysis. Results for other PCBs were not statistically significant
				PCB-118			
				9.4– < 14.3	64	0.90 (0.58–1.39)	
				14.3– < 22.1	78	1.12 (0.73–1.74)	
				≥ 22.1	104	1.60 (1.01–2.53)	
				PCB-156:			
				5.8–< 7.6	83	1.44 (0.91–2.26)	
				7.6–< 9.8	80	1.44 (0.90–2.31)	
				≥ 9.8	101	1.80 (1.11–2.94)	
				DL-PCBs (PCB-105, PCB-118, and PCB-156 in TEQ ng/kg)			
				4.2 to < 5.7	85	1.63 (1.04–2.55)	
				5.7 to < 7.4	78	1.45 (0.90–2.32)	
				≥ 7.4	102	2.02 (1.24–3.28)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Gammon *et al.* (2002), Long Island, New York, USA 1996–1997	646 cases 429 controls	Population based, matched by age	In-person interview and non-fasting blood sample Lipid-adjusted serum concentrations for 24 PCB congeners[c]	Quintiles of PCB concentration *(Sum of PCBs 118, 138, 153, and 180)*			Age, race, reproductive history, benign breast disease Interview response rates: cases, 83.2%; controls, 68.0%. No statistically significant results for other PCBs measured Results reported for four most common congeners. Numerous potential confounders investigated
				262.58–325.56	112	0.76 (0.51–1.15)	
				325.57–427.78	132	0.90 (0.60–1.35)	
				427.79–586.74	123	0.82 (0.54–1.24)	
				583.74–3287.34	126	0.83 (0.54–1.29)	
				PCB-118			
				32.66–46.45	133	0.96 (0.64–1.42)	
				46.46–63.39	109	0.77 (0.52–1.16)	
				63.40–94.94	114	0.82 (0.54–1.24)	
				94.95–1015.88	136	0.93 (0.60–1.43)	
				PCB-138			
				49.38–81.09	153	1.26 (0.85–1.88)	
				81.10–111.15	129	1.04 (0.69–1.55)	
				111.16–156.22	106	0.80 (0.52–1.21)	
				156.23–936.75	120	0.96 (0.63–1.48)	
				PCB-153			
				103.75–130.02	115	0.75 (0.50–1.13)	
				130.03–170.81	132	0.85 (0.57–1.27)	
				170.82–227.54	107	0.68 (0.45–1.03)	
				227.55–1130.08	132	0.86 (0.56–1.32)	
				PCB-180			
				51.49–69.70	121	0.87 (0.58–1.31)	
				69.71–87.41	117	0.81 (0.54–1.23)	
				87.42–120.37	128	0.89 (0.58–1.34)	
				120.38–721.29	134	0.95 (0.62–1.46)	

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Gatto *et al.* (2007), Los Angeles County, USA, 1994–1998	355 African-American women with histologically confirmed invasive breast cancer 327 controls	Population based, African-American women matched by age	Interview with structured questionnaire. Lipid-adjusted serum PCB concentration (congeners NR) measured by GC	Quintiles of total PCBs (μg/g) ≥ 0–0.38 > 0.38–0.47 > 0.47–0.60 > 0.60	 61 46 42 61	 1.06 (0.67–1.67) 0.82 (0.50–1.33) 0.76 (0.47–1.24) 1.01 (0.63–1.63)	Age, BMI, breastfeeding No statistically significant results by ER+/–, *p53*, or HER-2 status *P* for trend = 0.56
Itoh *et al.* (2009), Nagano Prefecture, Japan, 2001–2005	403 women aged 20–74 years with newly diagnosed invasive breast cancer 403 controls	Hospital-based	Self-administered questionnaire; hormone receptor status obtained from medical records; lipid-adjusted serum concentrations of 41 PCB congeners (ng/g lipid)	Total PCB quartiles (median) 110 160 200 290 *Highest vs lowest quartiles of exposure* PCB-153 PCB-138 PCB-180	 126 96 102 79 NR NR NR	 1.00 (ref) 0.79 (0.36–1.72) 0.57 (0.28–1.15) 0.33 (0.14–0.78) 0.40 (0.18–0.91) 0.61 (0.28–1.35) 0.29 (0.13–0.66)	Total lipid concentration in serum, BMI, reproductive risk factors, smoking, diet, medical history *P* for trend = 0.008 *P* for trend = 0.04 *P* for trend = 0.29 *P* for trend = 0.004
Zheng *et al.* (2000a), Connecticut, USA, 1994–1997	304 cases 186 controls	Hospital-based, with benign breast disease or normal tissue	Structured interview; lipid-adjusted breast adipose tissue concentrations of 9 PCB congeners[d] measured by GC (ng/g lipid)	Total PCBs 396.0–562.9 ≥ 563.0	 79 114	 0.6 (0.4–1.0) 0.7 (0.4–1.1)	Age, BMI, fat consumption, income, race, family history of breast cancer, and reproductive risk factors Participation rate: cases, 79%; controls, 74%. Stratification by type of breast disease, menopausal status, parity, lactation and body size showed no association with PCBs

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Zheng *et al.* (2000b), Connecticut, USA, 1995–1997	475 cases 502 controls	Hospital, with benign disease or population matched by age	Structured interview; lipid-adjusted serum concentrations of 9 PCB congeners[d] measured by GC (ng/g lipid)	Total PCBs 604.1–800.0 > 800.0	 160 160	 1.04 (0.76–1.45) 0.95 (0.68–1.32) *P* for trend = 0.41	Age, BMI, reproductive risk factors, HRT, dietary fat intake, family history of breast cancer, income, race, and study site When stratifying by parity, lactation and menopausal and ER status, no association was identified between PCBs and risk of breast cancer
Holford *et al.* (2000), Connecticut, USA, 1994–1997 (same population as Zheng *et al.*, 2000a)	304 cases 186 controls	Hospital-based	Breast adipose tissue analysed for 9 PCB congeners measured by GC (ng/g lipid)	*Linear logistic model* PCB-74 PCB-118 PCB-138 PCB-153 PCB-156 PCB-170 PCB-180 PCB-183 PCB-187 *Logistic ridge regression model* PCB-153 PCB-156 PCB-180 PCB-183		10-ppb change in exposure 0.93 (0.84–1.04) 1.04 (0.96–1.12) 1.04 (0.94–1.16) 0.87 (0.78–0.98) 0.79 (0.64–0.99) 0.85 (0.65–1.11) 1.14 (1.0–1.29) 1.82 (1.12–2.98) 1.11 (0.90–1.37) 0.98 (0.96–1.01) 0.87 (0.78–0.99) 1.02 (0.99–1.05) 1.23 (0.98–1.54)	Age, BMI, reproductive risk factors, dietary fat intake, income, fat concentrations of DDE See Zheng *et al.* (2000a) for details

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Zhang *et al.* (2004), Connecticut, USA, 1999–2002	374 Caucasian women 406 controls	Hospital- and population-based, matched by age	Structured in-person interview; lipid-adjusted serum concentrations of 9 PCB congeners[d] measured by GC (ng/g lipid) Genotyping of *CYP1A1 m1*, *m2*, and *m4* by PCR-RFLP	Total PCBs: 310–610 611–2600 *CYP 1A1 m2* genotype All women: Wildtype, low Wildtype, high Variants, low Variants, high Postmenopausal women: Wildtype, low Wildtype, high Variants, low Variants, high	 173 201 157 177 16 24 130 125 13 21	 1.00 (ref.) 1.2 (0.9–1.6) 1.00 (ref.) 1.2 (0.9–1.6) 1.6 (0.7–3.5) 3.6 (1.5–8.2) 1.0 1.1 (0.8–1.6) 1.8 (0.7–4.5) 4.3 (1.6–1.2)	See Zheng *et al.* (2000a, b) for details No significant association for *CYP1A1* m1 or m4 genotype or in premenopausal women
Rusiecki *et al.* (2004), Connecticut USA, 1994–97 (subgroup from same population as Zheng *et al.*, 2000a)	266 cases 347 controls	Hospital-based, benign breast disease	Interview; serum and breast adipose tissue analysed for 9 PCB congeners	*Total PCBs* ER+PR+ 394.31–558.69 > 558.69 ER–PR– 394.31–558.69 > 558.69 ER+PR- 394.31–558.69 > 558.69 ER–PR+ 394.31–558.69 > 558.69	 21 33 20 24 17 16 4 12	 0.6 (0.3–1.2) 0.6 (0.3–1.3) 0.5 (0.3–1.0) 0.5 (0.3–1.1) 1.0 (0.4–2.5) 0.6 (0.2–1.6) 0.2 (0.1–0.7) 0.5 (0.2–12.0)	Age, reproductive risk factors, BMI, family history of breast cancer in a first-degree relative Tumours were apparent with concentrations of PCB-183 (third tertile vs first: OR, 2.4; 95% CI, 1.0–6.0, *P* for trend = 0.03, but data not otherwise shown) Analyses for individual congeners did not show any association

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Stellman *et al.* (2000), Long Island, New York, USA, 1994–1996	232 cases 323 controls	Hospital	Structured interviews; 14 PCB congeners[e] in breast adipose tissue using GC	Total PCBs (ng/g) 181.82–332.24 > 332.24 PCB-156 5.87–13.59 > 13.60 PCB-183 3.16–5.66 > 5.67	 74 103 NR NR NR NR	 1.06 (0.67–1.69) 1.01 (0.60–1.69) 1.9 (1.1–3.0) 1.5 (0.9–2.5) 1.3 (0.8–2.1) 2.0 (1.2–3.4)	Age, BMI, race > 95% of eligible patients agreed to participate. Adipose tissue was obtained from 86% of all subjects. ORs for other PCB congeners, NR
Aronson *et al.* (2000), Ontario, Canada, 1995–1997	217 cases 213 controls	Hospital-based, cancer-free women, matched by age and study site	Telephone interview or mailed questionnaire; breast tissue analysed for 14 PCB congeners[b] expressed in µg/kg	*PCB-105* 4.2–6.1 6.2–12 ≥ 13 Premenopausal 4.2–6.1 > 6.1 Postmenopausal 4.2–6.1 > 6.1 *PCB-118* 17–27 28–49 ≥ 50 Premenopausal 17–27 > 27 Postmenopausal 17–27 > 27	 NR NR NR 12 30 25 86 NR NR NR 19 28 30 91	 1.16 (0.62–2.14) 2.03 (1.12–3.68) 3.17 (1.51–6.68) *P* for trend ≤ 0.01 1.29 (0.52–3.20) 3.91 (1.73–8.86) 0.98 (0.38–1.49) 1.49 (0.70–3.16) 1.25 (0.68–2.29) 1.88 (1.00–3.55) 2.31 (1.11–4.78) 1.04 (0.46–2.35) 2.85 (1.24–6.52) 1.39 (0.57–3.41) 1.58 (0.70–3.58)	Age, study site, HRT, ethnicity, family history of breast cancer, BMI, fat intake, alcohol intake, smoking, reproductive history Most controls were diagnosed with benign breast disease PCBs 28, 52, 101 and 128 were < LOD for > 30% of subjects and were not investigated

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
Aronson et al. (2000), (cont.)				*PCB-170*			
				24–34	NR	1.60 (0.92–2.78)	
				35–53	NR	1.09 (0.61–1.96)	
				≥ 54	NR	1.15 (0.60–2.22)	
				Premenopausal			
				24–34	24	0.83 (0.39–1.78)	
				> 34	25	0.89 (0.49–1.91)	
				Postmenopausal			
				24–34	51	3.27 (1.44–7.44)	
				> 34	76	1.63 (0.77–3.45)	
				PCB-180			
				52–71	NR	1.56 (0.90–2.70)	
				72–105	NR	1.21 (0.68–2.14)	
				≥ 106	NR	1.27 (0.66–2.46)	
				Premenopausal			
				52–714	26	1.07 (0.55–2.27)	
				> 71	23	0.89 (0.42–1.91)	
				Postmenopausal			
				52–714	46	2.43 (1.09–5.43)	
				> 71	80	1.77 (0.85–3.69)	
Aschengrau *et al.* (1998), Cape Cod, Massachusetts, USA, 1983–1986	261 incident cases 753 controls	Population, similar age and race	Structured interview, JEM and expert assessment	Possible or probable	5	3.2 (0.8–12.2).	Age, vital status, family history of breast cancer, age at first birth, personal history of prior breast cancer, benign breast disease, educational level and race PCB congeners to which cases were potentially exposed are not specified. Response rate: cases, 79%; controls, 74–81%

Table 2.10 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	OR (95% CI)	Covariates Comments
McElroy *et al.* (2004), Wisconsin, USA, 1998–2000	1481 cases 1301 controls	Population-based, of similar age	Telephone interview; consumption of sport-caught fish	*Recent consumption of sport-caught fish*			Age, family history of breast cancer, alcohol consumption, weight gain, weight at age 18 years, education, reproductive history
				Any	701	1.00 (0.86–1.17)	
				Premenopausal	286	1.24 (0.96–1.59)	
				Postmenopausal	388	0.91 (0.74–1.11)	
				Recent consumption of Great Lakes fish			
				Any	210	1.06 (0.84–1.33)	
				Premenopausal	95	1.70 (1.16–2.50)	
				Postmenopausal	104	0.78 (0.57–1.07)	

[a] The 20 PCB congeners were PCBs 8, 18, 28, 44, 52, 66, 77, 101, 105, 118, 126, 138, 148, 153, 170, 180, 187, 195, 206 and 209

[b] The 14 PCB congeners were PCBs 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187

[c] The 24 PCB congeners were PCBs 15, 28, 74, 66, 56, 101, 99, 82, 118, 146, 153, 105, 138, 178, 187, 183, 167, 174, 177, 156, 180, 170, 199, and 203

[d] The 9 congeners were PCBs 74, 118, 138, 153, 156, 170, 180, 183, and 187

[e] The 14 PCB congeners were PCBs 74, 99, 118, 138, 146, 153, 156, 167, 170, 172, 178, 180, 183, and 187

BMI, body mass index; CI, confidence interval; ER, estrogen receptor; GC, gas chromatography; HRT, hormone replacement therapy; Ile, isoleucine; JEM, job-exposure matrix; LOD, limit of detection; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PR, progesterone receptor; ref., reference; TEQ, toxic equivalent; Val, valine; vs, versus

In a study in Quebec City, Canada, in 17 women with cancer of the breast and 17 controls (Dewailly *et al.*, 1994), the concentration of PCB-99 was higher in the breast adipose tissue of women with ER-positive (ER+) infiltrating adenocarcinoma than in controls, while there were no significant differences for ER– women with cancer of the breast compared with controls, or for other PCB congeners or total PCBs.

In a study in Sweden, PCB concentrations were measured in non-tumour breast adipose tissue of 43 women with breast cancer and 35 controls (Liljegren *et al.*, 1998). Odds ratios adjusted for age and parity showed no association with concentrations of total PCB congeners in all subjects. However, among the subgroup of women with ER+ tumours, increased risk was observed for PCB-77 (OR, 33; 95% CI, 1.8–588) and PCB-126 [odds ratio not calculated as there were no unexposed cases].

In Hesse, Germany, concentrations of 12 PCB congeners in breast tissue from 45 women with cancer of the breast were compared with those in breast tissue from 20 women with benign breast disease: the average concentration of PCB-118 was significantly higher in the cases, with no statistical difference for other congeners (Güttes *et al.*, 1998).

A case–control study in eastern Slovakia included 24 cases of cancer of the breast diagnosed between 1997 and 1999 and 88 population controls, and measurements were made of 15 PCBs in serum (Pavuk *et al.*, 2003). Median concentrations of total PCBs were slightly higher among controls, and although odds ratios were less than unity, no finding was statistically significant.

In two reports of studies of 100 cases of cancer of the breast and 100 surgical controls in Belgium (Charlier *et al.*, 2003), concentrations of PCB-101 and PCB-153 were significantly higher for cases than controls. A second study of 60 cases and controls by the same authors reported an association only for PCB-153 (OR, 1.8; 95% CI, 1.4–2.5) after adjusting for age and reproductive risk factors (Charlier *et al.*, 2004). [It was not clear whether the same population was studied in both articles.]

In a case–control study in Mexico, 70 cases of cancer of the breast were compared with 70 hospital controls, and blood samples were taken for measurement of 20 PCB congeners (Recio-Vega *et al.*, 2011). An increased risk of cancer of the breast was apparent for total PCBs (OR, 1.09; 95% CI, 1.02–1.16) and for the exposure groups 2b (OR, 1.90; 95% CI, 1.25–2.88), 3 (OR, 1.81; 95% CI, 1.08–3.04), and 4 (OR, 1.57; 95% CI, 1.20–2.07) defined according to Wolff & Toniolo (1995). Elevated odds ratios were reported for several PCB congeners (PCB-118, PCB-128, PCB-138, PCB-170, PCB-180, PCB-187, PCB-195, PCB-206 and PCB-209) and risks were generally higher in postmenopausal women. [Although this was a small study, several increased risks were reported. However, the analytical approach was unclear to the Working Group and the age distribution was notably different in cases and controls, suggesting potential for residual confounding by age.]

Using a registry of banked serum collected between 1981 and 1987 from 63 Alaskan native women who subsequently developed cancer of the breast and 63 age-matched cancer-free women, analyses adjusting for ethnicity, family history of cancer of the breast, and parity showed no association with PCB exposure (Rubin *et al.*, 2006). In a study in Greenland of 31 cases of cancer of the breast and 115 controls, all of Inuit descent, some evidence of higher serum concentrations of PCBs was found for patients with cancer of the breast compared with controls; however, the odds ratios for total PCBs did not demonstrate any association (Bonefeld-Jørgensen *et al.*, 2011). [The populations included in these studies were of special interest due to their documented high exposures to PCBs.]

(b) *Larger studies of PCB concentrations in blood*

In a case–control study in western New York State, USA, 154 postmenopausal women with incident cancer of the breast and 192 postmenopausal community controls were compared in terms of serum concentrations of 73 detected congeners (Moysich *et al.*, 1998). No association with total PCBs, moderately chlorinated PCBs or highly chlorinated PCBs was found, but increased risk was apparent for less chlorinated PCBs above the detection limit (OR, 1.66; 95% CI, 1.07–2.88 for the combined second and third tertiles); among parous women who had never lactated the magnitude of risk was higher in association with total PCBs (OR, 2.87; 95% CI, 1.01–7.29) and moderately chlorinated PCBs (OR, 3.57; 95% CI, 1.10–8.60). In a subsequent study on PCBs and *CYP1A1* polymorphism (found to be induced by PCBs in experimental studies, see Section 4), no association with *CYP1A1* genotype was found among women with a low PCB body burden; among women with a PCB burden above the median for the control group, an increased risk of cancer of the breast was observed when at least one valine allele was present (OR, 2.93; 95% CI, 1.18–7.45) when compared with women who were homozygous for the isoleucine allele (Moysich *et al.*, 1999b). Adjustment for serum lipids and BMI did not affect the magnitude of this association. [Although not large, this study was rigorous in terms of design and implementation.]

Among patients of several ethnic groups in a hospital-based case–control study in New York City, USA, 175 patients with cancer of the breast and 355 control patients were frequency-matched by age and race/ethnicity (Wolff *et al.*, 2000b). Highly chlorinated and less chlorinated biphenyls and other chlorinated compounds were measured in serum, and the tumour markers ER, progesterone receptor (PR), *p53*, and erbB-2 were assessed. Concentration of PCBs was not associated with risk of cancer of the breast. Risk of cancer of the breast was not examined with respect to tumour stage or markers, but PCB concentrations did not differ according to these factors. [This was a high quality study notable for the number of tumour markers investigated, but the analysis focused largely on exposure markers, rather than exposure–disease associations.]

In a population-based case–control study of cancer of the breast in African-American and white women in North Carolina, USA, 748 cases and 659 controls were enrolled (Millikan *et al.*, 2000). Lipid-adjusted concentrations of 35 PCB congeners were measured in plasma, but detailed analyses were presented only for total PCBs. Odds ratios were adjusted for age and age squared, and additionally for race, menopausal status, BMI, parity/lactation, hormone replacement therapy, and income, depending on the stratification factors. Results were presented in strata of race, parity plus lactation, BMI and history of farming. Risk of cancer of the breast was increased with total PCB exposure among African-American women (third tertile OR, 1.74; 95% CI, 1.00–3.01), but not among white women (third tertile OR, 1.03; 95% CI, 0.68–1.56). This risk was particularly high for African-Americans with BMI > 34.2 (third tertile total PCBs, OR, 4.92; 95% CI, 1.63–14.83). [This was a large, high-quality study, and included African-Americans.]

In the same study population as Millikan *et al.* (2000), Li *et al.* (2005) investigated *CYP1A1* polymorphisms and their interaction with PCB exposure in relation to risk of cancer of the breast among the 612 cases and 599 controls who had provided blood. Results showed no evidence of joint effects between *CYP1A1* M1-containing genotypes and total PCBs for either race. Among white women, statistically significant multiplicative interactions were observed between *CYP1A1* M2-containing genotypes and total PCBs (P = 0.02), but the association between PCBs and cancer of the breast was inverse. A multiplicative interaction was suggested among African-American women between *CYP1A1*

M3-containing genotypes and total PCBs, with an odds ratio of 1.6 (95% CI, 0.8–3.2) for women with total plasma PCB concentrations ≥ 0.430 ng/mL and any *CYP1A1* M3 genotype compared with lower PCB concentration and no M3 genotype (*P* for interaction = 0.10). [This large study was able to assess interactions with *CYP1A1*.]

In a case–control study conducted in 1994–7 in Quebec City, Canada, plasma concentrations of 14 PCB congeners were measured in 314 women with cancer of the breast and 523 controls (219 hospital controls, 304 population controls) (Demers *et al.*, 2002). Analyses in relation to cancer of the breast excluded five congeners that were detected in < 70% of the women. The remaining PCB congeners were correlated (Pearson correlation coefficients, 0.29 to 0.96). Risk of cancer of the breast was associated with the highest quartile of concentration of PCB-118 (OR, 1.60; 95% CI, 1.01–2.53) and PCB-156 (OR, 1.80; 95% CI, 1.11–2.94). Among the subgroup of premenopausal women, the odds ratio for the highest quartile of concentration of PCB-118 was 2.87 (95% CI, 1.13–7.31), and for PCB-156 it was 2.90 (95% CI, 1.18–7.15). No significant increase in risk was seen in postmenopausal women. When PCB-105, PCB-118 and PCB-156 were grouped, higher concentration was associated with increased risk of cancer of the breast (OR, 2.02; 95% CI, 1.24–3.28), but the PCBs that were the most abundant (PCB-138, PCB-153 and PCB-180) were not associated with risk of cancer of the breast. An earlier publication from this study investigated associations between organochlorine compounds and cancer of the breast, specifically in relation to axillary-lymph-node involvement and tumour size (Demers *et al.*, 2000). PCB-153 was selected as a surrogate for all PCB congeners because it was the most abundant in plasma samples and was strongly correlated with other prevalent congeners ($r \geq 0.72$; $P < 0.0001$). The relative risk of having a tumour size ≥ 2 cm was increased, but not significantly, with increasing plasma concentration of PCB-153. However, a higher concentration of PCB-153 was significantly associated with increased risk among those with axillary lymph-node involvement (OR, 2.12; 95% CI, 1.05–4.30, adjusted for confounders) and when tumour size > 2 cm and node involvement were considered together, (OR, 3.51; 95% CI, 1.41–8.73), with an exposure–response trend. [This was a well-designed and well-implemented study with two control groups and stratification for menopausal status.]

In a large population-based case–control study of environmental exposures and cancer of the breast conducted in 1996–7 on Long Island, NY, USA, serum concentrations of 24 PCB congeners were measured for 646 cases and 429 controls, with results presented for the four most commonly occurring congeners (PCB-118, PCB-138, PCB-153 and PCB-180) (Gammon *et al.*, 2002). There was no association between cancer of the breast and the sum concentration of the four PCBs, or any specific congener, and there was no effect of lactation, menopausal status, stage of disease, or hormone receptor status. [This was a large, well-designed and well-implemented study.]

In a population-based case–control study of African-American women, serum concentrations of PCBs [congeners not specified] were measured in 355 cases and 327 controls (Gatto *et al.*, 2007). Risk of cancer of the breast was not associated with total PCBs (OR comparing highest with lowest quintile, 1.01; 95% CI, 0.64–1.63), and BMI, parity, breastfeeding, and menopausal status did not modify the measures of effect. PCBs were not associated with an increase in the risk of any subtype of cancer of the breast as defined by PR, ER, *p53*, or HER-2/*neu* status. [Statistical power was limited for subgroup analyses.]

In a hospital-based case–control study of cancer of the breast in Nagano, Japan, including 403 matched pairs collected from 2001 to 2005, serum concentrations of total PCBs were associated with decreased risk of cancer of the

breast for the highest versus lowest quartile of concentration of total PCBs (OR, 0.33; 95% CI, 0.14–0.78) (Itoh *et al.*, 2009). For the specific congeners PCB-153 and PCB-180, the odds ratios were 0.40 (95% CI, 0.18–0.91) and 0.29 (95% CI, 0.13–0.66), respectively. The trend in the inverse relationship persisted when results were stratified by hormone-receptor and menopausal status. [The Working Group was not able to explain the inverse associations reported in this study.]

(c) *Larger studies of PCB concentrations in blood and breast adipose tissue*

Five publications from a research group in Connecticut, USA, were informative, although their potential overlap was not clear. In 1994–1997, 304 cases of cancer of the breast and 186 controls aged 40–79 years were recruited and breast adipose tissue was analysed for nine PCB congeners (PCB-74, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183 and PCB-187) (Zheng *et al.*, 2000a). Age- and lipid-adjusted risk estimates were null in relation to total PCBs, PCB groups, and any of the congeners. Stratification by type of breast disease, menopausal status, parity, lactation, and body size showed null associations with concentrations of PCBs. From the same study population, Holford *et al.* (2000) calculated risk in relation to both linear logistic and logistic ridge regression analyses for nine PCB congeners by incremental (10 ng/g) changes in exposure: PCB-153 and PCB-156 were associated with decreased risk and PCB-180 and PCB-183 were associated with increased risk of cancer of the breast. In analyses using ridge regression and adjusting for covariates, no congeners remained associated with cancer of the breast. In another case–control study from this research group, subjects were recruited in 1995–1997 (overlap in years of study with Zheng *et al.*, 2000a): 475 incident cases of cancer of the breast were included, and 502 controls were randomly selected from the population or from patients with newly diagnosed benign breast disease at the same hospital (Zheng *et al.*, 2000b). Serum concentrations of nine PCB congeners were determined. After adjustment for confounding factors, all odds ratios were null. A related study focused on the potential interaction between CYP1A1 and lipid-adjusted serum concentrations of PCBs on risk of cancer of the breast among Caucasian women recruited in 1999–2002, with 374 cases and 406 controls (Zhang *et al.*, 2004). The odds ratio for high exposure (> 610 ng/g) to PCBs was 1.2 (95% CI, 0.9–1.6). With respect to *CYP1A1* genotype, the risks associated with higher serum concentration of total PCBs was highest for carriers of the *m2* variant genotype both among all women combined (OR, 3.6; 95% CI, 1.5–8.2), and in postmenopausal women (OR, 4.3; 95% CI, 1.6–12.0). No significant association was reported for *CYP1A1 m1* or *m4* genotypes or among premenopausal women. Finally, in another publication on a subset of 266 cases of cancer of the breast and 347 controls with benign breast disease, there was no association for total subjects, adjusted for standard risk factors, between cancer of the breast by joint ER/PR status and serum concentrations of total PCBs and adipose-tissue concentrations of nine PCB congeners (Rusiecki *et al.*, 2004). However, among postmenopausal women, increased risk of cancer of the breast was seen in relation to increased concentrations of PCB-183 among women with ER+PR+ tumours (third versus first tertile, OR, 2.4; 95% CI, 1.0–6.0; *P* for trend = 0.03). [While there appeared to be overlap between this group of studies from Connecticut, the extent of the overlap was difficult to determine, therefore the independence of the findings was not known. Controls were drawn from a mix of hospital and population sources, and the impact of this selection method was difficult to gauge. The large number of subgroup analyses, particularly in the study by Rusiecki *et al.* (2004), which presented 80 odds ratios, increased the probability of chance findings.]

(d) Larger studies of PCB concentrations in adipose tissue

On Long Island, New York, USA, concentrations of 14 PCB congeners in adipose tissue did not differ for 232 women with cancer of the breast and 323 hospital controls with benign breast disease or non-breast-related conditions, after adjustment for age, race, and BMI (Stellman *et al.*, 2000). No increase in risk was observed for total PCBs, but congeners PCB-156 and PCB-183 were associated with significantly increased risk (OR, 1.9; 95% CI, 1.1–3.0 for the second tertile of exposure distribution for PCB-156; and OR, 2.0; 95% 1.2–3.4 for the highest tertile of PCB-183). No other congener was associated with risk of cancer of the breast, and no clear difference in risk was seen for ER+ and ER– tumours. [This was a large, well-designed study, but results were only presented for total PCBs and two congeners.]

In a case–control study in Kingston and Toronto, Ontario, Canada, noncancerous breast adipose tissue collected before treatment from 217 incident cases of cancer of the breast and 213 controls undergoing biopsy was analysed for 14 PCB congeners (Aronson *et al.*, 2000). PCB-105 and PCB-118 were associated consistently with risk of cancer of the breast after adjusting for other factors (OR, 3.17; 95% CI, 1.51–6.68; and OR, 2.31; 95% CI, 1.11–4.78, respectively, for the fourth versus first quartile of the exposure distribution) and these effects increased monotonically. PCB-138 was also associated consistently with increased risk, but the odds ratios were imprecise. Stronger associations were apparent among premenopausal women (PCB-105: OR, 3.91; 95% CI, 1.73–8.86; and PCB-118: OR, 2.85; 95% CI, 1.24–6.52, for the highest exposure category). Among postmenopausal women, risks associated with PCB-170 and PCB-180 were also elevated in the second of three exposure groups (OR, 3.27; 95% CI, 1.44–7.44; and OR, 2.43; 95% CI, 1.09–5.43, respectively), but declined below significance in the highest group (ORs 1.63 and 1.77, respectively). No other PCB congener was significantly associated with risk. Although the odds ratios did not differ significantly by subtype of cancer, the odds ratios for total PCBs were higher for ER– than for ER+ cancer of the breast (Woolcott *et al.*, 2001). Investigation of specific genotype–PCB interactions among 68 cases and 52 controls with blood samples in this study showed increased risk of cancer of the breast for *CYP1A1* M1 wildtype homozygotes with high exposure to PCB-105 (OR, 3.20; 95% CI, 1.14–8.98) (McCready *et al.*, 2004). [This was a large, well-designed study.]

(e) Exposure estimates from occupational or dietary histories

A few case–control studies have estimated PCB exposures from occupational or dietary histories.

A population-based case–control study in Massachusetts, USA, included 261 incident cases of cancer of the breast diagnosed between 1983 and 1986 and 753 controls. The subjects were interviewed to ascertain all full-time jobs held since age 18 years. Probable exposure to PCBs was associated with non-significant increases in the risk of cancer of the breast (adjusted OR, 3.2; 95% CI, 0.8–12.2; five exposed cases and six exposed controls) (Aschengrau *et al.*, 1998). [The Working Group noted imprecise findings.]

Consumption of fish from the Great Lakes as a source of exposure to PCBs was investigated as a potential risk factor for cancer of the breast in a population-based case–control study in Wisconsin, USA (McElroy *et al.*, 2004). There were 1481 cases aged 20–69 years, diagnosed in 1998–2000 in the Wisconsin Cancer Reporting System, and 1301 controls of similar age were randomly selected from licensed drivers and Medicare lists; telephone interviews were used to obtain information on consumption of all sport-caught (Great Lakes and other lakes) fish and risk factors for cancer of the breast. After adjustment for risk factors, including age, education, weight,

alcohol consumption, reproductive history, and family history of cancer of the breast, no association was found between risk of cancer of the breast and recent consumption of sport-caught fish (OR, 1.00; 95% CI, 0.86–1.17), recent consumption of fish from the Great Lakes (OR, 1.06; 95% CI, 0.84–1.33), or the number of fish meals per year. Menopausal status appeared to be an effect modifier, with recent consumption of fish from the Great Lakes not associated with postmenopausal cancer of the breast (OR, 0.78; 95% CI, 0.57–1.07), but with premenopausal breast cancer (OR, 1.70; 95% CI, 1.16–2.50). [This was a large study with exposure assessment that used consumption of sport fish as a proxy for PCB exposure, but did not use biomarkers.]

(f) Combined analysis of five studies in the USA

The results of five case–control studies in the north-east USA conducted before 2000 (of which three are nested in cohort studies) (Moysich *et al.*, 1998; Helzlsouer *et al.*, 1999; Laden *et al.*, 2001a, b and Hunter *et al.*, 1997; Zheng *et al.*, 2000a, b; Wolff *et al.*, 2000b) and in which plasma or serum concentrations of PCBs were measured have been combined into an analysis of 1400 cases and 1642 controls using a standardized approach to confounder and effect-modification assessment, and a random-effects model to estimate associations (Laden *et al.*, 2001b). For women in the fifth quintile of lipid-adjusted values compared with those in the first quintile, the multivariate pooled odds ratio for cancer of the breast associated with the sum of PCBs (PCB-118, PCB-138, PCB-153 and PCB-180) was 0.94 (95% CI, 0.74–1.21). No consistent increase in risk was observed in subgroups defined by parity or lactation. [This combined analysis focused on the most prevalent PCBs that were analysed in all five studies; while this enhanced precision for the overall relationship, it did not show associations for specific PCB congeners and PCB subgroups. The Working Group noted that several informative studies were published after this combined analysis.]

2.3.3 Cancer of the prostate

Several epidemiological studies have investigated possible associations between cancer of the prostate and exposure to PCBs. These studies differed in study design (i.e. case–control studies, nested case–control studies) and in the assessment of PCBs (i.e. job-exposure matrices, measurement of PCB concentrations in blood or adipose tissue).

Seidler *et al.* (1998) described the results of a case-referent study including 192 patients with cancer of the prostate and 210 controls from medical practices or clinic in Germany. Occupational exposure to PCBs was estimated using a British job-exposure matrix (Pannett *et al.*, 1985). Most subjects had no or low exposure to PCBs and no association between exposure and risk of cancer of the prostate was reported. [Due to the relative low participation rate among controls (55%), selection bias could not be excluded. Furthermore, the validity of the job-exposure matrix was unknown and significant exposure misclassification could not be ruled out.]

Ritchie *et al.* (2003, 2005) conducted a hospital-based case–control study in Iowa, USA, in which 30 PCB congeners were measured in serum samples from 58 patients with cancer of the prostate and 99 age-matched controls. Odds ratios were elevated for total PCBs, and for PCB-153, and PCB-180. A monotonic, not statistically significant, exposure–response trend was observed for total PCBs. For PCB-180, the odds ratio was significantly increased (OR, 3.13; 95% CI, 1.33–7.34) only in the middle (but not the highest) category of exposure. [This study was small with multiple comparisons.]

In a population-based case–control study in Sweden, Hardell *et al.* (2006a) compared

concentrations of 37 PCB congeners in samples of fat tissue from 58 cases of cancer of the prostate and 20 controls with benign prostate hyperplasia. The odds ratio for the sum of PCBs and cancer of the prostate was 1.21 (95% CI, 0.42–3.50) in all men. PCB-153 was associated with an increased risk of cancer of the prostate (OR, 3.15; 95% CI, 1.04–9.54). Stronger associations were observed in men with prostate-specific antigen (PSA) > 16.5 ng/mL; the odds ratio was 1.91 (95% CI, 0.55–6.55) for total PCBs, and risks for enzyme and phenobarbital-inducing PCBs (Wolff *et al.*, 1997) and for less chlorinated PCBs (Moysich *et al.*, 1999a) were significantly increased in this subgroup of men. [This study was small and involved multiple comparisons.]

Aronson *et al.* (2010) conducted a case–control study among urology patients in Ontario, Canada. Concentrations of 14 PCB congeners were measured in serum of 79 men with incident cancer of the prostate and 329 age-matched controls. No association was observed between concentrations of individual PCB congeners or the sum of PCBs, and the risk of prostate cancer. [As both cases and controls underwent the same diagnostic procedures and were screened by PSA and digital rectal examination, selection bias was unlikely in this study].

2.3.4 Melanoma

(a) Cutaneous malignant melanoma

See Table 2.11

Gallagher *et al.* (2011) conducted a case–control study of 80 patients with malignant melanoma of the skin and 310 controls. The cases were part of a larger case–control study and were originally recruited to evaluate the effect of exposure to ultraviolet (UV) light and gene variants on risk of melanoma, and the controls were recruited using population-based registries. Lipid-adjusted plasma concentrations of 14 PCB congeners were determined and data were reported for 8, as well as for total PCBs, and dioxin-like and non-dioxin-like PCBs. Statistically significant associations with malignant melanoma were observed for the highest compared with the lowest quartile for: total PCBs (OR, 6.02; 95% CI, 2.0–18.17); summed non-dioxin-like PCBs (OR, 7.02; 95% CI, 2.30 –21.43); summed dioxin-like PCBs (OR, 2.84; 1.01–7.97), and all of the individual PCB congeners examined (PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183 and PCB-187). [The Working Group considered that, in light of its appropriate design and control of relevant potential confounders, this was a high-quality study, despite the relatively small sample size and being described as "preliminary" by the authors. The positive associations for all the individual PCB congeners may have been a result of correlations among congeners. Multiple comparisons were not formally addressed, but it is likely that adjustment for multiple comparisons would not change the interpretation of the results.]

(b) Uveal melanoma

See Table 2.11

In a multicentric case–control study in nine European countries, Behrens *et al.* (2010) investigated the association between risk of uveal melanoma and exposure to PCBs. The 293 men and women with uveal melanoma were frequency-matched to 3198 population and hospital controls by country, age, and sex. Exposure to transformer oils was assessed by questionnaire, with exposures to PCBs classified as "potential" or "confirmed," depending on whether subjects reported exposure to a named brand of oil with known PCB content. Analyses were adjusted for age, country, eye colour, and history of ocular damage from ultraviolet light. Only men reported exposure to transformer/capacitor oils. The odds ratio for any exposure was 2.74 (99.3% CI, 1.07–7.02), and was similar in magnitude for men with more than 10 years of exposure and for "confirmed" exposure. For exposure to Pyralene (the most frequently reported PCB-containing

Table 2.11 Case–control studies on melanoma and exposure to PCBs

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cutaneous malignant melanoma							
Gallagher *et al.* (2011) British Columbia, Canada, 2000–2004	80 310	Population	Lipid-adjusted concentrations of 14 PCBs[a] (units NR)				Age, sex, education, skin reaction to repeated sun exposure, and total recreational sun exposure
				Total PCBs			
				98.01–148.71	11	1.36 (0.45–4.09)	
				148.72–213.44	12	1.27 (0.39–4.12)	
				> 213.44	29	6.02 (2.00–18.17)	*P* for trend < 0.001
				DL-PCBs			
				9.37–15.10	8	0.31 (0.10–0.98)	
				15.11–22.57	16	1.16 (0.41–3.26)	
				> 22.57	25	2.84 (1.01–7.97)	*P* for trend = 0.003
				NDL-PCBs			
				86.68–133.66	12	2.05 (0.66–6.39)	
				133.67–192.39	11	1.19 (0.36–3.90)	
				> 192.39	30	7.02 (2.30–21.43)	*P* for trend < 0.001
				PCB-118			
				> 4.90–8.16	13	0.89 (0.34–2.34)	
				> 8.16–13.32	14	1.13 (0.40–3.23)	
				> 13.32–46.19	23	3.04 (1.05–8.74)	*P* for trend = 0.012
				PCB-138			
				> 12.79–20.76	19	1.89 (0.68–5.28)	
				> 20.76–30.65	8	1.30 (0.37–4.56)	
				> 30.65–104.49	28	4.91 (1.69–14.32)	
				PCB-153			
				> 27.75–42.07	14	2.01 (0.70–5.77)	
				> 42.07–60.43	12	1.35 (0.43–4.25)	
				> 60.43–735.90	27	4.86 (1.68–14.08)	*P* for trend = 0.002
				PCB-156			
				> 4.09–6.07	13	1.04 (0.36–2.97)	
				> 6.07–8.65	13	1.48 (0.49–4.45)	
				> 8.65–113.32	29	4.22 (1.51–11.78)	*P* for trend = 0.001

Table 2.11 (continued)

Reference, study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Gallagher et al. (2011) British Columbia, Canada, 2000–2004 (cont.)				*PCB-170*			
				> 7.97–12.16	13	1.50 (0.53–4.29)	
				> 12.16–18.51	13	1.10 (0.32–3.77)	
				> 18.51–901.52	29	4.60 (1.60–13.22)	*P* for trend = 0.001
				PCB-180			
				> 25.20–38.16	12	1.46 (0.49–4.37)	
				> 38.16–59.40	14	1.55 (0.44–5.43)	
				> 59.40–3786.60	30	5.89 (1.87–18.50)	*P* for trend = 0.001
				PCB-183			
				> 1.87–84.86	54	4.27 (1.71–10.68)	
				PCB-187			
				> 6.64–10.45	11	2.54 (0.75–8.58)	
				> 10.45–16.10	15	2.56 (0.76–8.62)	
				> 16.10–833.15	30	11.47 (3.32–39.68)	*P* for trend < 0.001
Uveal melanoma							
Behrens *et al.* (2010), Denmark, France, Germany, Italy, Latvia, Portugal, Sweden, Spain, UK Jan 1994–Dec 1997	293 3198	Hospital and population	Questionnaire on occupational exposure	Exposure to oils potentially containing PCBs			Country, age, ocular damage due to UV, eye colour, exposure to high-voltage installations ORs were Bonferroni-corrected for seven independent tests to control for multiple comparisons, thus all CI are 99.3%. Response rates: cases, 84%; hospital, 84%; population controls, 61% Only men were exposed to oils
				Never exposed	150	1.00	
				Ever exposed	6	2.74 (0.72–10.37)	
				Duration > 10 years	2	2.62 (0.29–24.06)	
				"Confirmed" exposure to PCB oil	4	2.61 (0.54–12.63)	
				Exposure to Pyralene	4	6.43 (1.17–35.30)	

[a] The 14 PCB congeners were PCBs 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187.

CI, confidence intervals; DL-PCB, dioxin-like PCB; NDL-PCB, non-dioxin-like PCB; OR, odds ratio; PCB, polychlorinated biphenyl; UK, United Kingdom; UV, ultraviolet

oil), the odds ratio was 6.43 (99.3% CI, 1.17–35.30; four cases). [This study was notable in being the only large study of a rare cancer. Multiple comparisons were addressed via adjusted 99.3% confidence intervals, but exposure was rare and estimates were imprecise.]

2.3.5 Other cancers

(a) Urothelial cancer

Steineck *et al.* (1990) carried out a population-based case-referent study of urothelial cancer in men in Stockholm, Sweden. Occupational exposures to PCBs and several other agents were assigned by an industrial hygienist. The adjusted odds ratio for estimated exposure to PCBs was 3.3 (95% CI, 0.6–18.4). [The precision of this study was quite limited and the definition of the cancer sites was broad.]

(b) Cancer of the testis

Hardell *et al.* (2003) analysed 38 PCB congeners in blood samples collected from 61 incident cases of cancer of the testis and 58 age-matched controls from the Swedish population registry. No association between cancer of the testis and the sum of PCB concentrations in blood was found. Mothers of 44 cases and 45 controls also provided blood samples; significantly higher PCB concentrations were found for mothers of cases compared with mothers of controls (OR, 3.8; 95% CI, 1.4–10). A difference in the sum of PCBs between mothers of cases and mothers of controls was also reported in two subsequent publications by the same authors (Hardell *et al.*, 2004, 2006b). [Due to the timing of blood collection of the mothers, which was decades after the cases' births, the interpretation of these results was difficult. PCB concentrations in women may be affected by weight changes, child bearing, lactation, and subsequent exposure. Thus it could not be assumed that the concentrations measured in women at the time of the study were representative of their sons' exposures in utero.]

(c) Cancer of the lung

Recio-Vega *et al.* (2012) investigated the association between PCB concentrations, *CYP1A1* polymorphisms and the risk of cancer of the lung in a case–control study in northern Mexico including 43 cases of cancer of the lung and 86 controls without cancer who were recruited from two hospitals. Information including history of exposure to PCBs was collected through in-person interview and 20 PCB congeners were measured in serum. Odds ratios were adjusted for age, agricultural occupation, and tobacco smoking. There was a significant association between PCB-18 and cancer of the lung (OR, 1.13; 95% CI, 1.04–1.38). Odds ratios for PCB-52, PCB-118, and PCB-170 were similar in magnitude, but did not reach statistical significance, while odds ratios for other congeners were close to unity. *CYP1A1* polymorphism was not associated with serum concentrations of total PCBs. [The Working Group noted that this study provided information about less chlorinated PCBs, which are rarely measured; however, the etiological relevance of measurements of PCBs of short half-life was questionable. In addition, the methods used for subject recruitment and for statistical analysis were not clearly described, and the possibility of residual confounding by age was noted.]

(d) Cancer of the colorectum

Howsam *et al.* (2004) assessed associations between cancer of the colorectum and exposure to PCBs and gene–environment interactions in 132 cases and 76 controls sampled from a larger hospital-based case–control study in Barcelona, Spain. Serum concentrations of PCB-28, PCB-52, PCB-101, PCB-118, PCB-138, PCB-153, and PCB-180 were measured. Point mutations in *K-ras* and *p53* genes and expression of p53 protein were assessed in tumour tissue. PCB-28 and PCB-118 were significantly associated with an increased risk of cancer of the colorectum (ORs, 2.75;

95% CI, 1.29–5.83; and 2.02; 95% CI, 1.00–4.08, respectively), for the more exposed category. A statistically significant exposure–response trend was observed for the mono-*ortho* PCB group that combined PCB-28 and PCB-118 (*P* for trend = 0.004). Odds ratios for the other PCBs were not consistently or significantly increased. No significant interaction of mono-*ortho* PCBs with *p53* or *K-ras* mutations was found. [The use of controls representing several diagnostic groups and control for potential confounding factors were strengths of this study. However, the case definition combining cancers of the colon and rectum may mix diseases with potentially different etiologies.]

(e) Cancer of the pancreas

In a population-based case–control study of cancer of the pancreas in the San Francisco area, USA, Hoppin *et al.* (2000) analysed 11 PCB congeners in serum samples from 108 cases of cancer of the pancreas and 82 controls matched by sex and age-group. Total lipid-adjusted PCB concentrations were estimated using the sum of all congeners. A statistically significant dose–response relationship ($P < 0.001$) was observed for total PCBs, with an odds ratio of 4.2 (95% CI, 1.8–9.4) for ≥ 360 versus < 185 ng/g. Significantly elevated odds ratios were also observed for the highest tertiles of PCB-153 (OR, 3.0; 95% CI, 1.4–6.6) and PCB-180 (OR, 8.4; 95% CI, 3.4–21). Odds ratios remained elevated after adjusting for dichlorodiphenyldichloroethylene (DDE) content, and in a sensitivity analysis of the effects of bioconcentration. [A strength of the study was that the issue of confounding by bioconcentration in fat due to adipose-tissue loss was addressed. Nevertheless, the small number of subjects limited a clear interpretation of the results.]

(f) Cancer of the biliary tract

Ahrens *et al.* (2007) investigated the association between cancer of the extrahepatic biliary tract and occupational exposure to endocrine-disrupting compounds in a European multicentre case–control study of 183 men with histologically confirmed carcinoma of the extrahepatic biliary tract and 1938 matched controls. Self-reported job descriptions were converted to semiquantitative indicators of occupational exposure to 14 types of suspected endocrine-disrupting compounds, including PCBs, hormones, phthalates, and pesticides. Odds ratios were adjusted for age, country, and history of gallstones. The adjusted odds ratio for cancer of the extrahepatic biliary tract and ever-exposure to PCBs was 2.8 (95% CI, 1.3–5.9). When exposure intensity was analysed, the highest odds ratio was observed in the low-intensity category. [These results were based on a small number of exposed cases and trends were inconsistent.]

(g) Childhood cancer

Ward *et al.* (2009) conducted a population-based case–control in California, USA of 184 children aged 0–7 years with acute lymphocytic leukaemia and 212 controls from birth certificates matched by birth date, sex, race, and ethnicity. Concentrations of six PCB congeners in residential carpet dust were used as an exposure indicator. The odds ratio for detection of any PCB in dust was 1.97 (95% CI, 1.22–3.17) and the odds ratio for the highest quartile of total PCBs compared with the lowest was 2.78 (95% CI, 1.41–5.48). Significant exposure–response trends were reported for PCB-118, PCB-138 and PCB-153. [The study was well-designed and the method of exposure assessment used was a strength. The authors were able to rule out confounding by several organochlorine pesticides. The Working Group was unable to replicate the *P* values for trend tests.]

(h) Cancer of the endometrium

Sturgeon *et al.* (1998) conducted a multicentric hospital-based case–control study of cancer of the endometrium in five areas of the USA. Serum concentrations of 27 PCB congeners were measured for 90 individually matched case–control pairs. No associations were observed between elevated serum concentrations of several PCB groups, including total PCBs and potentially estrogenic PCBs, and risk of cancer of the endometrium. [The results did not appear to be affected by selection bias, but precision was limited.]

Weiderpass *et al.* (2000) measured serum concentrations of 10 PCB congeners in a population-based case–control study of 154 cases of cancer of the endometrium and 205 controls in Sweden. After adjustment there was no increase in risk associated with high concentrations of any of the congeners evaluated, and there were no significant trends in risk. [The power of this study was limited due to the small number of subjects. However, selection bias was unlikely, as the main reason for non-participation was the failure of the hospital staff to collect blood samples before surgery.]

Hardell *et al.* (2004) conducted a hospital-based case–control study with 76 cases and 39 controls to evaluate the risk of cancer of the endometrium associated with environmental endocrine disruptors. Concentrations of 37 PCB congeners were measured in adipose tissue. No association was found for the sum of PCBs or for any grouping of PCBs by structure or activity. [The power of this study was limited due to the small number of subjects.]

(i) Cancer of the male breast

Occupational risk factors for cancer of the male breast were investigated in a multicentric study of 104 cases and 1901 controls in eight European countries (Villeneuve *et al.*, 2010). Lifetime work history was obtained by in-person interviews, and potential occupational exposures including to PCBs were assessed using expert judgment. Results were reported for PCBs and dioxins combined, for which the fully-adjusted odds ratio was 1.6 (95% CI, 0.7–3.7). [This study had limited power to detect excess risk.]

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3. CANCER IN EXPERIMENTAL ANIMALS

In previous evaluations in 1978, 1979, 1987, and 2012 (IARC, 1978, 1979, 1987, 2012), the Working Group concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of polychlorinated biphenyls (PCBs). New data have since become available, and these have been taken into account in the present evaluation.

3.1 Oral administration

See Table 3.1 and Table 3.2

3.1.1 Individual PCBs and binary mixtures

The United States National Toxicology Program (NTP) has conducted a series of studies to evaluate the carcinogenicity of some PCB congeners administered alone or as binary mixtures in female Harlan Sprague-Dawley rats treated by gavage.

(a) PCB-126

Rat

Groups of 81 female Harlan Sprague-Dawley rats (age, 8 weeks) were given the dioxin-like congener PCB-126 at a dose of 0 (vehicle control), 30, 100, 175, 300, 550, or 1000 ng/kg body weight (bw) by gavage in corn oil : acetone (99 : 1), 5 days per week, for up to 104 weeks (core study) (Brix *et al.*, 2004; Nyska *et al.*, 2004; Walker *et al.*, 2005; Yoshizawa *et al.*, 2005, 2007, 2009; NTP, 2006a). Ten rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was given PCB-126 at a dose of 1000 ng/kg bw in corn oil : acetone (99 : 1) by gavage for 30 weeks, then the vehicle only for the remainder of the study. There were treatment-related increases in the incidences of cholangiocarcinoma and hepatocellular adenoma in rats treated with PCB-126 at doses of 300 ng/kg bw or higher, and 550 ng/kg bw or higher, respectively, for up to 104 weeks. There were three hepatocholangiomas in the group at 1000 ng/kg bw, and single incidences of cholangioma in the groups at 550 and 1000 ng/kg bw. [These tumours are rare, and it was uncertain whether they were related to treatment.] There were also statistically significant, dose-related increases in the incidences of a spectrum of non-neoplastic lesions that collectively were diagnosed as toxic hepatopathy. Significant increases in the incidence of cystic keratinizing epithelioma of the lung occurred in rats at 550 ng/kg bw or higher, and non-statistically significant low incidences of squamous cell carcinoma of the lung were also observed at the highest doses in the core-study groups. Gingival squamous cell carcinomas were observed in all exposure groups, and incidence was significantly increased in the group at 1000 ng/kg bw (core study). Adenomas and/or carcinomas were present in the adrenal cortex of rats in most groups, including the stop-exposure group, with a positive trend in the incidence of adenoma or carcinoma (combined) with increasing dose.

Table 3.1 Studies of carcinogenicity in rats exposed to PCBs and related compounds

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Individual PCBs and binary mixtures				
Harlan Sprague-Dawley (F) 104 wk NTP (2006a)	Core study: PCB-126 in corn oil : acetone (99 : 1) by gavage at doses of 0, 30, 100, 175, 300, 550, or 1000 ng/kg bw, 5 days/wk, for 104 wk 81 rats/group Stop-exposure study: PCB-126 at 1000 ng/kg for 30 wk followed by vehicle for the remainder of the study 50/group Interim evaluations: 10 rats per core study group were evaluated at wks 14, 31, and 53	*Liver* Cholangiocarcinoma (includes multiple): 0/53, 0/55, 1/53, 0/53, 5/53, 6/51, 22/53; 0/53, 2/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 0/53, 4/51, 15/53; 0/53, 0/50 (stop-exposure) Hepatocellular adenoma[a] (includes multiple): 1/53, 2/55, 1/53, 0/53, 2/53, 4/51, 7/53; 1/53, 0/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 0/53, 0/51, 1/53; 0/53, 0/50 (stop-exposure) Hepatocholangioma[b] (includes multiple): 0/53, 0/55, 0/53, 0/53, 0/53, 0/51, 3/53; 0/53, 0/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 0/53, 0/51, 1/53; 0/53, 0/50 (stop-exposure) Cholangioma[b]: 0/53, 0/55, 0/53, 0/53, 0/53, 1/51, 1/53; 0/53, 0/50 (stop-exposure) *Lung* Cystic keratinizing epithelioma (includes multiple): 0/53, 0/55, 0/53, 0/53, 1/53, 11/51**, 35/51*; 0/53, 0/50 (stop-exposure) Multiple: 0/53, 0/55, 0/53, 0/53, 0/53, 8/51*, 30/51*; 0/53, 0/50 (stop-exposure) Squamous cell carcinoma: 0/53, 0/55, 0/53, 0/53, 0/53, 1/51, 2/51; 0/53, 0/50 (stop-exposure)	$P < 0.001$ (1000 ng/kg bw) $P < 0.001$ (trend) $P \leq 0.001$ (1000 ng/kg bw) $P = 0.033$ (1000 ng/kg bw) $P < 0.001$ (trend) $P < 0.001$ (trend) NS NS *$P < 0.001$ **$P = 0.002$ $P < 0.001$ (trend) *$P \leq 0.001$ NS	Purity, 99% The overall incidence values are presented, but statistical analyses are based on the poly 3 test used by NTP that takes survival differences into account *Non-neoplastic lesions* Liver: toxic hepatopathy that included hepatocyte hypertrophy and hyperplasia, bile duct and oval cell hyperplasia, nodular hyperplasia, cholangiofibrosis, multinucleated hepatocytes, diffuse fatty change, bile duct cyst, necrosis, pigmentation, inflammation, portal fibrosis Lung: squamous metaplasia, and bronchiolar metaplasia of the alveolar epithelium No tumours were observed at interim evaluations at wk 14 and 31

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague-Dawley (F) 104 wk NTP (2006a) (cont.)		*Oral mucosa* Gingival squamous cell carcinoma[c]: 0/53, 1/55, 1/53, 1/53, 2/53, 2/53, 7/53*; 0/53, 2/50 (stop-exposure) *Adrenal cortex* Adenoma: 0/52, 1/55, 1/53, 0/53, 0/53, 1/52, 2/53; 0/52, 2/50 (stop-exposure) Carcinoma: 0/52, 1/55, 0/53, 0/53, 1/53, 0/52, 2/53; 0/52, 1/50 (stop-exposure) Adenoma or carcinoma (combined): 0/52, 2/55, 1/53, 0/53, 1/53, 1/52, 4/53; 0/52, 3/50 (stop-exposure)	*P = 0.010 P < 0.001 (trend) NS NS P = 0.022 (trend)	
Harlan Sprague-Dawley (F) 105 wk NTP (2006b)	Core study: PCB-153 in corn oil : acetone (99 : 1) by gavage at doses of 0, 10, 100, 300, 1000 or 3000 µg/kg bw by gavage, 5 days/wk for 105 wk 80–82 rats/group Stop-exposure study: 3000 µg/kg bw for 30 wk followed by vehicle for the remainder of the study 50/group Interim evaluations: 10 rats per core study group were evaluated at 14, 31, and 53 wk	*Liver* Cholangioma: 0/53, 0/54, 0/53, 0/53, 2/53, 0/51; 0/53, 2/50 (stop-exposure) Hepatocellular adenoma: 0/53, 0/54, 0/53, 0/53, 0/53, 1/51; 0/53, 0/50 (stop-exposure) *Thyroid gland* Follicular cell adenoma: 0/51, 0/52, 0/53, 0/53, 0/53, 0/51; 0/51, 2/49 (stop-exposure) *Interim evaluation (wk 53)* *Thyroid gland* Follicular cell adenoma: 0/10, 0/10, 1/10, 0/10, 0/10, 0/10	NS NS NS NS	Purity, 99% *Non-neoplastic lesions* Liver: hepatocyte hypertrophy, bile duct hyperplasia, oval cell hyperplasia, fatty change and pigmentation Thyroid gland: folicular cell hypertrophy Ovary and oviduct: chronic active inflammation Uterus: suppurative inflammation No tumours were observed at 14 and 31 wk

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague-Dawley (F) 105 wk NTP (2010)	Core study: PCB-118 by gavage in corn oil : acetone (99 : 1) at doses of 0, 100, 220, 460, 1000 or 4600 µg/kg bw, by gavage 5 days/wk for 105 wk. 80/group Stop-exposure study: 4600 µg/kg bw for 30 wk followed by vehicle only for the remainder of the study 50/group Interim evaluations: 10 rats per core-study group were evaluated at 14, 31, and 53 wk	*Liver* Cholangiocarcinoma (includes multiple): 0/52, 0/51, 0/52, 0/52, 3/52, 36/49; 0/52, 29/49 (stop-exposure) Multiple: 0/52, 0/51, 0/52, 0/52, 0/52, 30/49; 0/52, 17/49 (stop exposure) Hepatocellular adenoma (includes multiple): 0/52, 1/51, 1/52, 4/52, 12/52, 24/49; 0/52, 1/49 (stop-exposure) Multiple: 0/52, 0/51, 0/52, 0/52, 4/52, 14/49; 0/52, 1/49 (stop-exposure) Hepatocellular carcinoma: 0/52, 0/51, 0/52, 0/52, 0/52, 1/49; 0/52, 0/49 (stop-exposure) Hepatocholangioma: 0/52, 0/51, 0/52, 0/52, 0/52, 4/49; 0/52, 0/49 (stop-exposure) *Lung* Cystic keratinizing epithelioma (includes multiple): 0/51, 0/52, 0/52, 0/52, 0/52, 20/50; 0/51, 0/50 (stop-exposure) Multiple: 0/51, 0/52, 0/52, 0/52, 0/52, 8/50; 0/51, 0/50 (stop-exposure) *Uterus* Carcinoma[d]: 2/52, 2/52, 1/52, 3/52, 4/52, 3/52; 2/52, 11/50 (stop-exposure)	$P < 0.001$ (4600 µg/kg and stop-exposure) $P < 0.001$ (trend) $P \leq 0.001$ (4600 µg/kg) $P < 0.001$ (1000 and 4600 µg/kg) $P < 0.001$ (trend) $P \leq 0.01$ (4600 µg/kg) NS $P < 0.001$ (trend) $P < 0.001$ (4600 µg/kg) $P < 0.001$ (trend) $P \leq 0.05$ (4600 µg/kg) $P = 0.014$ (stop-exposure)	Purity, > 99% PCB-118 was analysed for the presence of PCDDs, PCDFs, and PCBs; trace amounts of TCDD (0.000005%), TCDF (0.000005%), PCB-126 (0.0000170%), PCB-169 (0.0000003%) and various other PCB congeners were found. The calculated total non-PCB-118 TEQ contribution was 0.39 ng TEQ/1000 µg of PCB-118 bulk test article *Non-neoplastic lesions* Liver: toxic hepatopathy that included hepatocyte hypertrophy and hyperplasia, bile duct and oval cell hyperplasia, nodular hyperplasia, cholangiofibrosis, multinucleated hepatocytes, diffuse fatty change bile duct cyst, necrosis, pigmentation, inflammation, portal fibrosis Lung: alveolar epithelium, metaplasia; bronchiolar epithelium, squamous metaplasia Adrenal cortex: atrophy and hyperplasia Thyroid gland: follicular cell, hypertrophy Nose: respiratory epithelium, hyperplasia

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague-Dawley (F) 105 wk NTP (2010) (cont.)		Squamous cell carcinoma: 0/52, 0/52, 3/52, 1/52, 1/52, 0/52; 0/52, 1/50 (stop exposure)	NS	
		Pancreas		Pancreas: acinus, cytoplasmic vacuolization
		Acinar adenoma: 0/52, 0/52, 0/52, 2/52, 3/52, 1/47; 0/52, 0/49 (stop-exposure)	NS	Nose: inflammation
		Acinar adenoma or carcinoma (combined): 0/52, 0/52, 0/52, 2/52, 3/52, 2/47; 0/52, 0/49 (stop exposure)	NS	Kidney: pigmentation No tumours were observed at interim evaluations at wk 14 and 31.
		Interim evaluation (wk 53)		
		Liver		
		Cholangiocarcinoma (includes multiple): 0/8, 0/8, 0/10, 0/8, 0/8, 3/8		
		Hepatocellular adenoma: 0/8, 0/8 0/10, 0/8, 0/8, 1/8		
Harlan Sprague-Dawley (F) 105 wk NTP (2006c)	*Constant-ratio study:* PCB-126 and PCB-153 as binary mixture with PCB-126 at doses of 0, 10, 100, 300, 1000 ng/kg bw per day, and PCB-153 at 0, 10, 100, 300, 1000 µg/kg bw per day in corn oil : acetone (99 : 1) by gavage *Varying-ratio study:* PCB-126 and PCB-153 as binary mixture at doses of PCB-126 at 300, 300, 300 ng/kg bw per day, and PCB-153 at 100, 300, 1000 µg/kg bw per day by gavage in corn oil : acetone 80–81/group *Interim evaluations:* 10 rats per core-study group were evaluated at wk 14, 31, and 53	*Constant-ratio study:* *Liver* Hepatocellular adenoma: 0/53, 0/53, 3/52, 5/52, 27/51*	*$P < 0.001$ $P < 0.001$ (trend)	Purity, > 99% (PCB-126 and PCB-153) *Non-neoplastic lesions* Liver: toxic hepatopathy that included hepatocyte hypertrophy and hyperplasia, bile duct and oval cell hyperplasia, nodular hyperplasia, cholangiofibrosis, multinucleated hepatocytes, diffuse fatty change bile duct cyst, necrosis, pigmentation, inflammation, portal fibrosis Lung: alveolar epithelium, metaplasia; bronchiolar epithelium, squamous metaplasia Adrenal cortex: atrophy and hyperplasia Thyroid gland: follicular cell hypertrophy Oral mucosa: gingival squamous hyperplasia
		Multiple: 0/53, 0/53, 0/52, 0/52, 16/51*	*$P \leq 0.01$	
		Hepatocellular carcinoma: 0/53, 0/53, 0/52, 0/52, 2/51	NS	
		Cholangiocarcinoma: 0/53, 0/53, 1/52, 9/52*, 30/51**	*$P \leq 0.05$ **$P \leq 0.01$	
		Multiple: 0/53, 0/53, 1/52, 5/53*, 21/52**	*$P \leq 0.05$ **$P \leq 0.01$ $P \leq 0.001$ (trend)	
		Hepatocholangioma: 0/53, 0/53, 0/52, 2/52, 6/51*	*$P = 0.012$ $P \leq 0.001$ (trend)	
		Multiple: 0/53, 0/53, 0/52, 0/52, 16/51*	*$P \leq 0.01$	

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague-Dawley (F) 105 wk NTP (2006c) (cont.)		*Lung* Cystic keratinizing epithelioma: 0/53, 0/53, 0/52, 1/53, 11/52* Multiple: 0/53, 0/53, 0/52, 0/53, 8/52* Squamous cell carcinoma: 0/53, 0/53, 0/52, 1/53, 1/52 *Oral mucosa* Squamous cell carcinoma: 0/53, 0/53, 2/53*, 5/53, 9/53** *Pancreas, acinus* Adenoma: 0/53, 1/53, 1/52, 3/52, 1/50 Adenoma or carcinoma (combined): 0/53, 1/53, 1/52, 4/52, 2/50 *Uterus* Squamous cell carcinoma[c]: 1/53, 1/53, 1/53, 4/53, 0/53 *Adrenal cortex* Adenoma: 0/53, 0/53, 0/52, 1/52, 1/51 *Varying-ratio study:* *Liver* Hepatocellular adenoma: 2/50, 5/52, 21/51 Multiple: 2/50, 0/52, 7/51 Cholangiocarcinoma: 7/50, 9/52, 25/51 Multiple: 1/50, 5/52, 13/51 Hepatocholangioma: 0/53, 0/50, 2/52, 2/51	*$P < 0.001$ $P < 0.001$ (trend) *$P \leq 0.01$ NS *$P = 0.031$ **$P = 0.002$ $P < 0.001$ (trend) NS NS NS NS $P \leq 0.001$ NR $P \leq 0.001$ NR NR	Pancreas acinus atrophy and cytoplasmic vacuolization For the varying-ratio study, note that *P* values represent a trend test across the three groups of PCB-126/PCB-153 mixtures and indicated the significance of the effect of increasing the proportion of PCB-153 in the mixture

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague-Dawley (F) 104 wk NTP (2006d)	*Core study:* PCB-126 and PCB-118 by gavage as binary mixture at doses of PCB-126 at 0, 62, 187, 622, 1866 or 3110 ng/kg bw per day, and PCB-118 at 0, 10, 30, 100, 300 or 500 µg/kg bw per day, in corn oil : acetone (99 : 1). [0, 7, 22, 72, 216 or 360 ng TEQ/kg bw] *Stop-exposure study:* PCB-126/PCB-118 at 3110 ng//500 µg/kg bw for 30 wk and then vehicle only for the remainder of the study. 81–86/group *Interim evaluations:* 10 rats per core study group were evaluated at 14, 31 and 53 wk	*Liver* Cholangiocarcinoma: 0/53, 0/51, 5/53, 19/53, 28/53, 12/65; 0/53, 19/50 (stop exposure) Multiple: 0/53, 0/51, 1/53, 12/53, 21/53, 72/65; 0/53, 12/50 (stop-exposure) Hepatocellular adenoma: 2/53, 1/51, 0/53, 4/53, 17/53, 5/65; 2/53, 1/50 (stop exposure) Multiple: 0/53, 0/51, 0/53, 2/53, 10/53, 2/65; 0/53, 0/50 (stop exposure) Hepatocellular carcinoma: 0/53, 0/51, 0/53, 0/53, 1/53, 0/65; 0/53, 0/50 (stop exposure) Hepatocholangioma: 0/53, 0/51, 0/53, 1/53, 1/53, 1/65; 0/53, 1/50 (stop exposure) Cholangioma: 0/53, 0/51, 0/53, 1/53, 0/53, 0/65; 0/53, 0/50 (stop exposure) *Lung* Cystic keratinizing epithelioma: 0/53, 0/51, 0/53, 20/53, 49/53, 41/66; 0/53, 12/50 (stop-exposure) Multiple: 0/53, 0/51, 0/53, 14/53, 48/53, 35/66; 0/53, 5/50 (stop exposure)	$P < 0.001$ (≥ 72 ng TEQ), $P < 0.001$ (trend) $P < 0.001$ (stop-exposure) $P \leq 0.05$ (≥ 72 ng TEQ) $P < 0.001$ (216 ng), $P = 0.021$ (360 ng) $P < 0.001$ (trend) $P \leq 0.001$ (216 ng) NS NS NS $P < 0.001$ (≥72 ng TEQ), $P < 0.001$ (trend) $P < 0.001$ (stop-exposure) $P \leq 0.01$ (≥ 72 ng TEQ) $P \leq 0.05$ (stop-exposure)	PCB-118, purity, > 98.5% (0.6% PCB-126; 0.2% PCB-77; 0.55% PCB-167) No animals in the core-study groups receiving the two higher doses survived to the end of the study, and survival in the stop-exposure group was significantly lower than in the vehicle-control group. Mean body weights in groups receiving PCB-126/PCB-118 at 622 ng/100 µg/kg bw or more were lower than in the vehicle-control groups throughout most of the study *Non-neoplastic lesions* Liver: the spectrum and severity of effects at the interim and 2-year time-points increased with dose and duration of exposure. At the end of the study in all groups receiving PCBs, there were significantly increased incidences and severity of toxic hepatopathy characterized by hepatocyte hypertrophy, multinucleated hepatocytes, pigmentation, diffuse fatty change, nodular hyperplasia, centrilobular fibrosis, cholangiofibrosis, oval cell hyperplasia, bile duct cyst, bile duct hyperplasia, and portal fibrosis

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Harlan Sprague-Dawley (F) 104 wk NTP (2006d) (cont.)		*Oral mucosa* Gingival squamous cell carcinoma: 1/53, 1/51, 2/53, 4/53, 0/53, 1/66; 1/53, 1/50 (stop-exposure) *Interim evaluation (at 53 wk)* *Lung* Cystic keratinizing epithelioma: 0/8, 0/7, 0/8, 1/8, 5/8, 0/0	NS $P \leq 0.05$ (216 ng TEQ)	Lung: bronchiolar metaplasia of the alveolar epithelium, squamous metaplasia, serosal fibrosis, and (in the stop-exposure group) keratin cysts Oral mucosa: gingival squamous hyperplasia
Known mixtures of PCBs				
Wistar (M) 120 d Rao & Banerji (1988), Silberhorn *et al.* (1990)	Aroclor 1260 at 0, 50, 100 ppm in the diet 32/group	Liver neoplastic nodules [tumours]: 0/32, 24/32*, 16/32*	*$P < 0.02$	Purity, NR *Non-neoplastic lesions:* adenofibrosis, centrilobular hypertrophy, individual hepatocyte necrosis, and vacuolated hepatocytes
F344 (M, F) 105 wk NTP (1978), Ward (1985), Morgan *et al.* (1981)	Aroclor 1254 at 0, 25, 50, 100 ppm in diet 24 M + 24 F per group	Hepatocellular adenoma: 0/24, 1/24, 2/24, 5/24* (M) 0/24, 0/24, 3/24, 2/24 (F) Hepatocellular carcinoma: 0/24, 0/24, 0/24, 2/24 (M) 0/24, 0/24, 0/24, 0/24 (F) Hepatocellular adenoma or carcinoma (combined): 0/24, 1/24, 2/24, 7/24* (M) 0/24, 0/24, 3/24, 2/24 (F) Adenocarcinoma of the glandular stomach: 0/47, 1/48, 3/48, 2/48 (M + F) Lymphoma or leukaemia: 3/24, 2/24, 5/24, 9/24 (M)	*$P < 0.05$ NS *$P < 0.05$ NS $P = 0.009$ (trend)	Chlorination, 54.67%; impurities not identified or quantitated Survival in males: controls, 92%; lowest dose, 83%; intermediate dose; 58%; highest dose, 46%. All females survived to the end of the bioassay *Non-neoplastic lesions* Liver: pigmented macrophages with cytoplasmic crystalline structures and hepatocellular degeneration Stomach: gastric intestinal metaplasia in males and females; gastric intestinal metaplasia and adenocarcinoma commonly coexist and may share initiating mechanisms

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague-Dawley (M, F) 24 mo Mayes *et al.* (1998), Faroon *et al.* (2001), Brown *et al.* (2007)	In the diet: Aroclor 1016: 0, 50, 100, 200 ppm Aroclor 1242: 0, 50, 100 ppm Aroclor 1254: 0, 25, 50, 100 ppm Aroclor 1260: 0, 25, 50, 100 ppm Treated: 50 M + 50 F/group Controls: 100 M + 100 F/group	*Liver (M)* *Aroclor 1016:* Hepatocellular adenoma: 4/100, 1/50, 1/50, 2/50 Hepatocellular carcinoma: 3/100, 1/50, 1/50, 2/50 Total liver tumours: 7/100, 2/50, 2/50, 4/50 *Aroclor 1242:* Hepatocellular adenoma: 4/100, 1/50, 3/50 Hepatocellular carcinoma: 3/100, 1/50, 1/50 Total liver tumours: 7/100, 1/50, 4/50 *Aroclor 1254:* Hepatocellular adenoma: 4/100, 2/50, 2/50, 6/50 Hepatocellular carcinoma: 3/100, 2/50, 2/50, 0/50 Total liver tumours: 7/100, 4/50, 4/50, 6/50 *Aroclor 1260:* Hepatocellular adenoma: 4/100, 2/50, 5/50, 7/50* Multiple: 0/100, 0/50, 2/50, 3/50 Hepatocellular carcinoma: 3/100, 1/50, 1/50, 3/50 Multiple: 0/100, 0/50, 0/50, 1/50 Hepatocholangioma: 0/100, 0/50, 0/50, 2/50 Total liver tumours: 7/100, 3/50, 6/50, 10/50*	 NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS *$P \leq 0.05$ NS NS NS NS *$P \leq 0.05$	Purity, NR Total liver tumours include hepatocellular adenoma and carcinoma, hepatocholangioma and hepatocholangiocarcinoma Liver toxicity was distinctly more severe in females than in males. Non-neoplastic lesions observed in the liver: centrilobular hypertrophy, bile duct hyperplasia, hepatocyte vacuolization, and basophilic, clear cell, eosinophilic, and mixed cell foci In males given Aroclor 1242, 1254, or 1260, there were non-statistically significant increases in the incidence of follicular cell hyperplasia

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague-Dawley (M, F) 24 mo Mayes et al. (1998), Faroon et al. (2001), Brown et al. (2007) (cont.)		*Liver (F)* *Aroclor 1016:* Hepatocellular adenoma: 1/100, 1/50, 5/50*, 5/50* Multiple: 0/100, 0/50, 1/50, 3/50 Hepatocellular carcinoma: 0/100, 0/50, 1/50, 0/50 Total liver tumours: 1/100, 1/50, 6/50*, 5/50** *Aroclor 1242:* Hepatocellular adenoma: 1/100, 10/50*, 12/50* Multiple: 0/100, 3/50*, 7/50** Hepatocellular carcinoma: 0/100, 0/50, 2/50 Hepatocholangioma: 0/100, 1/50, 2/50 Hepatocholangiocarcinoma: 0/100, 1/50, 0/50 Total liver tumours: 1/100, 11/50*, 15/50* *Aroclor 1254:* Hepatocellular adenoma: 1/100, 18/50*, 26/50*, 27/50* Multiple: 0/100, 9/50*, 15/50*, 21/50* Hepatocellular carcinoma: 0/100, 0/50, 4/50*, 6/50** Multiple: 0/100, 0/50, 1/50, 4/50*	 *$P \leq 0.05$ $P \leq 0.05$ (trend) NS *$P \leq 0.01$ **$P \leq 0.05$ *$P \leq 0.01$ *$P \leq 0.05$ **$P \leq 0.01$ NS NS NS *$P \leq 0.01$ *$P \leq 0.01$ *$P \leq 0.01$ *$P \leq 0.05$ **$P < 0.01$ *$P \leq 0.05$	

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague-Dawley (M, F) 24 mo Mayes et al. (1998), Faroon et al. (2001), Brown et al. (2007) (cont.)		Hepatocholangioma: 0/100, 2/50, 6/50*, 1/50	*$P \leq 0.01$	
		Total liver tumours: 1/100, 19/50*, 28/50*, 28/50*	*$P \leq 0.01$	
		Aroclor 1260:		
		Hepatocellular adenoma: 1/100, 9/50*, 10/50*, 21/50*	*$P \leq 0.01$	
		Multiple: 0/100, 6/50*, 8/50*, 16/50*	*$P \leq 0.01$	
		Hepatocellular carcinoma: 0/100, 1/50, 1/50, 5/50*	*$P \leq 0.01$	
		Multiple: 0/100, 0/50, 0/50, 1/50	NS	
		Hepatocholangioma: 0/100, 0/50, 0/50, 3/50*	*$P \leq 0.05$	
		Total liver tumours: 1/100, 10/50*, 11/50*, 24/50*	*$P \leq 0.01$	
		Thyroid gland (M)		
		Aroclor 1016:		
		Follicular cell adenoma: 1/100, 3/50, 2/50, 0/50	NS	
		Follicular cell carcinoma: 1/100, 1/50, 1/50, 1/50	NS	
		Total thyroid tumours: 2/100, 4/50, 3/50, 1/50	NS	
		Aroclor 1242:		
		Follicular cell adenoma: 1/100, 5/50*, 5/50*	*$P \leq 0.05$	
		Follicular cell carcinoma: 1/100, 2/50, 1/50	NS	
		Total thyroid tumours: 2/100, 7/50*, 6/50**	*$P \leq 0.01$ **$P \leq 0.05$	

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
CR Sprague-Dawley (M, F) 24 mo Mayes et al. (1998), Faroon et al. (2001), Brown et al. (2007) (cont.)		*Aroclor 1254:* Follicular cell adenoma: 1/100, 6/50*, 4/50**, 5/50** Follicular cell carcinoma: 1/100, 1/50, 3/50, 1/50 Total thyroid tumours: 2/100, 7/50*, 7/50*, 6/50** *Aroclor 1260:* Follicular cell adenoma: 1/100, 6/50*, 4/50*, 3/50 Follicular cell carcinoma: 1/100, 1/50, 1/50, 1/50 Total thyroid tumours: 2/100, 7/50*, 5/50**, 4/50 *Mammary gland (F)* *Aroclor 1254:* Fibroadenoma: 34/100, 22/50, 29/50*, 10/50	*$P \leq 0.01$ **$P \leq 0.05$ NS *$P \leq 0.01$ **$P \leq 0.05$ *$P \leq 0.01$ NS *$P \leq 0.01$ **$P \leq 0.05$ *$P \leq 0.01$	
Sprague-Dawley (M, F) 29 mo Norback & Weltman (1985)	Feed containing Aroclor 1260 (mixed with corn oil) at 100 ppm for 16 mo, then at 50 ppm for an additional 8 mo, and then the control diet for an additional 5 mo. Controls received basal diet with added corn oil for 18 mo, then the basal diet only for 10 mo The medial and left lobes of the liver of 10 rats (2 M and 2 F controls, and 3 M and 3 F PCB-treated rats, for each period) were removed (partial hepatectomy) at 1, 3, 6, 9, 12, 15, and 18 mo Control: 63/group (M, F) Aroclor 1260: 70/group (M, F)	*Liver* Neoplastic nodule: 0/32, 5/46 (M); 1/49, 2/47 (F) Trabecular carcinoma: 0/32, 2/46 (M); 0/49, 19/47 (F) Adenocarcinoma: 0/32, 0/46 (M); 0/32, 24/47 (F) Cholangioma (simple): 2/32, 14/46 (M); 2/49, 21/47 (F) Cholangioma (cystic): 0/32, 2/46 (M); 1/49, 5/47 (F)	NS $P < 0.0001$ (F) $P < 0.0001$ (F) $P = 0.01$ (M) $P < 0.0001$ (F) NS	Purity, NR Some adenocarcinoma-bearing rats also had trabecular carcinoma (not included in the incidence of trabecular carcinoma) PCB-exposed rats developed hepatocellular lesions in the following sequence: centrilobular cell hypertrophy at 1 mo, foci of cell alteration at 3 mo, areas of cell alteration at 6 mo, neoplastic nodules at 12 mo, trabecular carcinoma at 15 mo, and adenocarcinoma at 24 mo

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Wistar (M) Up to 832 days Schaeffer *et al.* (1984), Faroon *et al.* (2001)	Basic diet for 8 wk, then: Group 1: basic diet; 139 rats (controls) Group 2: basic diet supplemented with Clophen A 30 at 100 ppm; 152 rats Group 3: basic diet supplemented with Clophen A 60 at 100 ppm; 141 rats After 801 days, randomly selected rats from all three groups were killed daily up to day 832	Hepatocellular neoplastic nodules: 5/131, 38/130*, 63/126* Hepatocellular carcinoma: 1/131, 4/130, 61/126* Thymoma: 16/131, 4/130, 2/129 Other neoplasms: 88/131, 66/138, 33/129	*$P < 0.05$ *$P < 0.05$ NS NS	Purity of Clophen A 30, 99.1%; purity of Clophen A 60, 99.9% Over the first 800 days on study, total mortality in groups 2 and 3 was significantly lower than in group 1 (controls) Hepatic foci of cellular alteration were observed in all groups, but were more frequent in the treated groups. There was a trend from foci to neoplastic nodules to hepatocellular carcinoma. Other non-neoplastic hepatic lesions observed in control and treated groups included bile duct hyperplasia The results of a re-evaluation of the hepatocellular tumours using contemporary diagnostic criteria and nomenclature were in general consistent with the original evaluation (Moore *et al.*, 1994) Tumour data were reported in six 100-day periods; the data reflected incidences from day 1 until day 832
Sherman (F) 22 mo Kimbrough *et al.* (1975), Moore *et al.* (1994)	Diets containing Aroclor 1260 at 0 or 100 ppm for up to 21 mo 200/group	*Liver* Hepatic neoplastic nodules: 0/173, 144/184 Hepatocellular carcinoma: 1/173, 26/184	$P < 0.0001$ $P < 0.0001$	Purity, NR The incidences of the hepatocellular lesions were re-evaluated by a panel of pathologists using contemporary diagnostic criteria and nomenclature (Moore *et al.*, 1994). Lesions that had been previously diagnosed as neoplastic nodules were now classified as either hepatocellular hyperplasia or hepatocellular adenoma. In general, the results were consistent between the original evaluation and the re-evaluation

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence and/or multiplicity of tumours	Significance	Comments
Donryu (M, F) ≤ 560 days Kimura & Baba (1973), Silberhorn *et al.* (1990)	Diets containing Kanechlor 400 (in olive oil) at 38.5 ppm for 4 wk, then, based on bw-gain, the initial concentration was sequentially increased: 2× for 8 wk 4× for 3 wk 8× for 3 wk 16× for 8 wk, decreased to 12× for 32 wk because bw decreased markedly; two 4-wk periods with no treatment during this time Controls were fed powdered diet mixed with pure olive oil Controls: 5 M + 5 F/group Treated: 10 M + 10 F/group	Liver adenomatous nodules: 0/5, 0/10 (M); 0/5, 6/10 (F) Adrenal gland adenoma: 0/5, 0/10 (M); 0/5, 1/10 (F)	 $P = 0.044$ (F) NS	Purity, NR Multiple small nodules observed in the livers of females, but not males Fatty degeneration observed in the liver of all dosed groups, but only in two females in the control groups Study may have been limited by short duration, small number of rats/group, and may have exceeded the maximum tolerated dose The Working Group noted that current terminology for adenomatous nodules is hepatocellular adenoma

[a] Historical controls: 4/371 (1.1% ± 1.5%); range, 0–4%
[b] Historical controls: 0/371
[c] Historical controls: 4/371 (1.1% ± 1.0%); range, 0–2%
[d] Historical controls: 6/473 (1.3% ± 1.4%); range, 0–4%
[e] Historical controls: 1/371 (0.3% ± 0.7%); range, 0–2%

bw, body weight; F, female; M, male; mo, month; NR, not reported; NS, not significant; PCB, polychlorinated biphenyl; wk, week; yr, year

Table 3.2 Studies of carcinogenicity in mice exposed to PCBs and related compounds

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence of tumours	Significance	Comments
C57BL/6, B6D2F1 or DBA/2 (M) 44 wk Beebe *et al.* (1995)	Initiation with a single intraperitoneal dose of NDEA, 90 mg/kg bw, in tricaprylin, or tricaprylin only, and promoted 3 wk later ± Aroclor 1254 (100 ppm) in the diet for 20 wk 18–39/group	*Tricaprylin only, or tricaprylin + Aroclor 1254:* C57BL/6 mice: Liver tumours (all types): 0/27, 0/27 Lung tumours: 1/27, 1/27 B6D2F1 mice: Liver tumours (all types): 0/31, 2/34 Lung tumours: 0/31, 2/34 DBA/2 mice: Liver tumours (all types): 0/23, 0/24 Lung tumours: 3/31, 1/24	 NS NS NS	Purity, NR
dd (M, F) 24 or 32 wk Nagasaki *et al.* (1975)	Diet containing Kanechlor 300, 400 or 500 for 24 or 32 wk 24-wk study: Kanechlor 400 (0, 100, 250 ppm) or Kanechlor 500 (0, 100, 250 ppm) 32-wk study: Kanechlor 300 (0, 100, 250, 500 ppm) Kanechlor 400 (0, 100, 250, 500 ppm) Kanechlor 500 (0, 100, 250, 500 ppm) 20/group	*Hepatocellular carcinoma, 24 wk study:* Kanechlor 400: 0/20, 0/20, 0/20 (M) Kanechlor 500: 0/20, 0/20, 0/20 (M) *Hepatocellular carcinoma, 32-wk study:* Kanechlor 300: 0/20, 0/19, 0/19, 0/20 (M); 0/12, 0/19, 0/20, 0/20 (F) Kanechlor 400: 0/20, 0/17, 0/19, 0/20 (M); 0/12, 0/20, 0/20, 0/17 (F) Kanechlor 500: 0/20, 0/18, 0/20, 9/17*(M); 0/12, 0/19, 0/20, 4/17*(F)	 NS NS NS NS *$P < 0.05$	Purity, NR Other proliferative lesions observed in the liver of mice treated with Kanechlor 400 or 500 included oval cell hyperplasia, bile duct proliferation, cellular hypertrophy and nodular hyperplasia
BALB/cJ (M) 11 mo Kimbrough & Linder (1974), Faroon *et al.* (2001)	Diets containing Aroclor 1254 (mixed with corn starch) at 0 or 300 ppm for 6 mo, followed by basal diet for 5 mo, or Aroclor 1254 at 0 or 300 ppm for 11 mo Group 1: control diet for 6 mo Group 2: Aroclor 1254 for 6 mo Group 3: control diet for 11 mo Group 4: Aroclor 1254 for 11 mo 50/group	*Hepatoma* 6 mo: 0/24, 1/24, 11 mo: 0/34, 10/22	 NS $P < 0.001$	Purity, NR The Working Group noted that "hepatoma" is not a nomenclature currently used in toxicological pathology. In studies before 1978, the term "hepatoma" may have been used to denote benign or malignant liver tumours. In this study it was not clear whether hepatoma referred to a benign or malignant hepatic tumour

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence of tumours	Significance	Comments
dd (M) 32 wk Ito *et al.* (1973), Silberhorn *et al.* (1990), Faroon *et al.* (2001)	Basal diet supplemented with Kanechlor for 32 wk: Kanechlor 300 at 0, 100, 250 or 500 ppm Kanechlor 400 at 0, 100, 250 or 500 ppm Kanechlor 500 at 0, 100, 250 or 500 ppm 12 mice/treated group; 6 controls	*Liver* *Kanechlor 300* Nodular hyperplasia: 0/6, 0/12, 0/12, 0/12 Hepatocellular carcinoma: 0/6, 0/12, 0/12, 0/12 *Kanechlor 400* Nodular hyperplasia: 0/6, 0/12, 0/12, 0/12 Hepatocellular carcinoma: 0/6, 0/12, 0/12, 0/12 *Kanechlor 500* Nodular hyperplasia: 0/6, 0/12, 0/12, 7/12* Hepatocellular carcinoma: 0/6, 0/12, 0/12, 5/12*	 NS NS NS NS *[P<0.05] *[NS]	Purity: Kanechlor 300: 59.8% trichlorobiphenyl, 23.0% tetrachlorobiphenyl, 16.6% dichlorobiphenyl, 0.6% pentachlorobiphenyl Kanechlor 400: 43.8% tetrachlorobiphenyl, 32.8% trichlorobiphenyl, 5.8% pentachlorobiphenyl, 4.6% hexachlorobiphenyl, 3.0% dichlorobiphenyl Kanechlor 500: 55.0% pentachlorobiphenyl, 26.5% tetrachlorobiphenyl, 12.8% hexachlorobiphenyl, 5.0% trichlorobiphenyl The description of nodular hyperplasias provided was not sufficiently detailed to determine whether these hyperplastic nodules were benign hepatocellur adenomas according to current nomenclature Other histopathological changes in mice treated with PCBs included oval cell proliferation, bile duct proliferation and hepatocyte hypertrophy. Amyloid deposition was also observed in the livers of mice fed diets containing various commercial PCB mixtures at 100 or 250 ppm

d, day; mo, month; NDEA, *N*-nitrosodiethylamine; NR, not reported; NS, not significant; PCB, polychlorinated biphenyl; wk, week; yr, year

(b) PCB-153

Rat

Groups of 80–82 female Harlan Sprague-Dawley rats (age, 8 weeks) were given the di-*ortho*-substituted non-dioxin-like congener PCB-153 (purity, 99%) at a dose of 0 (81 rats; vehicle control), 10, 100, 300, 1000, or 3000 µg/kg bw, in corn oil:acetone (99 : 1) by gavage, 5 days per week, for up to 105 weeks (core study) (Yoshizawa *et al.*, 2005, 2007, 2009; NTP, 2006b). Ten rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was given PCB-153 at 3000 µg/kg bw corn oil : acetone (99 : 1) by gavage for 30 weeks, and then the vehicle only for the remainder of the study. At 2 years, cholangiomas occurred in two rats at 1000 µg/kg bw and in two rats in the stop-exposure group. A single hepatocellular adenoma was observed in the group at 3000 µg/kg bw. Cholangioma did not occur in the historical vehicle controls (0 out of 371) of the NTP studies. [One factor limiting interpretation of effects in this bioassay was that the highest dose of PCB-153 used (3000 µg/kg bw) was chosen to match the highest dose used in an NTP bioassay with a mixture of PCB-126 and PCB-153 (NTP, 2006c), rather than on the basis of the results of a previous short-term study of toxicity. There was no effect of PCB-153 at 3000 µg/kg bw on survival or body weight in this 2-year study, suggesting that higher doses would probably have been tolerated. In a tumour-promotion study in F344 female rats, Dean *et al.* (2002) gave PCB-153 at a dose of 10 000 µg/kg bw by gavage, three times per week, for 8 weeks, and observed only a significant increase in liver weight.]

(c) PCB-118

Rat

Groups of 80 female Harlan Sprague-Dawley rats (age, 8 weeks) were given PCB-118 (purity, > 99%) at a dose of 0 (vehicle control), 100, 220, 460, 1000, or 4600 µg/kg bw in corn oil : acetone (99 : 1) by gavage, 5 days per week, for up to 105 weeks (core study) (Yoshizawa *et al.*, 2009; NTP, 2010). Ten rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was given PCB-118 at a dose of 4600 µg/kg bw in corn oil : acetone (99 : 1) by gavage for 30 weeks, then the vehicle for the remainder of the study. At the 53-week interim evaluation, three cholangiocarcinomas and one hepatocellular adenoma were observed in the group at 4600 µg/kg bw. At 2 years, the incidences of multiple cholangiocarcinoma, and single or multiple cholangiocarcinoma (combined) in the group at 4600 µg/kg bw and the stop-exposure group were significantly greater than those in the vehicle-control group. The incidences of multiple hepatocellular adenoma in the group at 4600 µg/kg bw, and single or multiple hepatocellular adenoma (combined) in the groups at 1000 µg/kg bw or 4600 µg/kg bw were significantly greater than those in the vehicle-control group. Four rats developed hepatocholangioma and one rat developed hepatocellular carcinoma in the group at 4600 µg/kg bw. Significantly increased incidences of multiple cystic keratinizing epithelioma of the lung and of single or multiple cystic keratinizing epithelioma (combined) occurred in the group at 4600 µg/kg bw compared with the vehicle-control group. The incidence of uterine carcinoma in the stop-exposure group was significantly greater than that in the vehicle-control group; a slight increase in the incidence of squamous cell carcinoma of the uterus occurred in the group at 220 µg/kg bw, and single incidences occurred at 460 µg/kg bw, 1000 µg/kg bw, and in the stop-exposure group. There were slightly increased incidences of exocrine pancreatic adenoma in core-study groups receiving PCB-118 at doses of 460 µg/kg bw or higher.

Table 3.3 Description of binary mixtures of PCB-126 and PCB-153 given to rats in a study of carcinogenicity by the NTP (2006c)

Group	Total TEQ (ng TEQ/kg bw)	Mass	
		PCB-126 (ng/kg bw)	PCB-153 (μg/kg bw)
Constant ratio mixture			
1	Vehicle control	0	0
2	1	10	10
3	10	100	100
5	30	300	300
7	100	1000	1000
Varying ratio mixture			
1	Vehicle control	0	0
4	30	300	100
5	30	300	300
6	30	300	1000

PCB, polychlorinated biphenyl; TEQ, toxic equivalent

(d) PCB-126 and PCB-153

Rat

The NTP conducted a 2-year study that was designed to assess the carcinogenicity of a mixture of PCB-126 and PCB-153 in a constant ratio, and a mixture of PCB-126 and PCB-153 in varying ratios to assess the effect of increasing PCB-153 (NTP, 2006c; Yoshizawa *et al.*, 2009). Groups of 81 or 80 female Harlan Sprague-Dawley rats (age, 8 weeks) received a mixture of PCB-126 and PCB-153 in corn oil : acetone (99 : 1) by gavage, 5 days per week, for up to 105 weeks. Dose groups were referred to by the total concentrations of toxic equivalents (TEQ) provided by the PCBs in the mixture per kg bw in each group (see Table 3.3); a control group of 81 female rats received the corn oil : acetone vehicle only (group 1). Ten rats per group were evaluated at 14, 31, and 53 weeks. At 2 years, the incidences of hepatocellular adenoma (single or multiple) in group 7 (constant ratio; TEQ, 100 ng/kg bw), and of cholangiocarcinoma (single or multiple) in group 5 (constant ratio; TEQ, 30 ng/kg bw) or group 7 were significantly increased. The incidence of hepatocholangioma was also significantly increased in group 7. Two rats in group 7 had hepatocellular carcinoma; no hepatocellular carcinoma was reported in the historical vehicle controls. In the varying-ratio study, increasing the proportion of PCB-153 significantly increased the incidences of hepatocellular adenoma and cholangiocarcinoma. In the constant-ratio study, the incidence of cystic keratinizing epithelioma of the lung was significantly increased in group 7. In addition, one squamous cell carcinoma was reported in group 5 and one in group 7. Significantly increased incidences of gingival squamous cell carcinoma of the oral mucosa occurred in groups 5 and 7. There was also a slight increase in the incidence of uterine squamous cell carcinoma in group 5.

(e) PCB-118 and PCB-126

Rat

Groups of 81 female Harlan Sprague-Dawley rats (age, 9 weeks) were given a binary mixture of PCB-118 and PCB-126 (see Table 3.4) at a dose of 0 (vehicle control), 7, 22, 72, 216 ng TEQ/kg bw, by gavage in corn oil : acetone (99 : 1), 5 days per week, for up to 104 weeks; a group of 86 female rats received the mixture at a dose of 360 ng TEQ/kg bw (Yoshizawa *et al.*, 2005, 2007,

Table 3.4 Composition of a mixture of PCB-118 and PCB-126 given to rats in a study of carcinogenicity by the NTP (2006d)

	PCB-118	PCB-126	PCB-77[a]	PCB-167[a]
Percentage of bulk mass[b]	98.5	0.6	0.2	0.5
Percentage of total TEQ[c]	13.7	86.3	0.03	0.007

[a] Present as contaminants that were not considered to contribute to the dioxin-like activity of the bulk synthesized test article
[b] Based on the level of each compound present in the bulk synthesized test article
[c] Assuming WHO toxic equivalency factor (TEF) values of 0.1 (PCB-126), 0.0001 (PCB-118), 0.0001 (PCB-77) and 0.00001 (PCB-167)
PCB, polychlorinated biphenyl; TEQ, toxic equivalent

2009; NTP, 2006d). Ten rats per group were evaluated at 14, 31, or 53 weeks. In the stop-exposure group, 50 female rats received the mixture at a dose of 360 ng TEQ/kg bw for 30 weeks, and then the vehicle only for the remainder of the study. The dose groups are described in Table 3.5. The mixture contained predominantly PCB-118 (by mass) and PCB-126 (by TEQ), but also contained PCB-77 and PCB-167 as contaminants that were not considered to contribute to the dioxin-like activity of the bulk synthesized material (see Table 3.4).

No rats at 216 or 360 ng TEQ/kg bw survived to the end of the study; survival in the stop-exposure group was also significantly lower than in the vehicle-control group, with only 10 rats surviving to the end of the study. Mean body weights of rats receiving 72 ng TEQ/kg bw or more were lower than those of rats in the vehicle-control group throughout most of the study. At 2 years, the incidences of cholangiocarcinoma (single or multiple, combined) and cholangiocarcinoma (multiple) were significantly increased in groups receiving 72 ng TEQ/kg bw or more. The incidence of hepatocellular adenoma was also significantly increased in the groups at 216 and 360 ng TEQ/kg bw. In addition, single occurrences of hepatocholangioma, cholangioma, or hepatocellular carcinoma were observed in some groups receiving 72 ng TEQ/kg bw or more. At 53 weeks, the incidence of cystic keratinizing epithelioma of the lung was significantly increased in the group at 216 ng TEQ/kg bw. At 2 years, significantly increased incidences of cystic keratinizing epithelioma (single or multiple, combined) and of cystic keratinizing epithelioma (multiple) were reported in groups receiving 72 ng TEQ/kg bw or more. Non-statistically significant increased incidences of gingival squamous cell carcinoma of the oral mucosa were observed at the end of the 2-year study.

3.1.2 Commercial mixtures of PCBs

(a) Aroclor 1254

(i) Mouse

In a study on the activity of Aroclor 1254 in mice with different aryl hydrocarbon receptor (AhR) phenotypes, groups of 23–34 male C57BL/6, DBA/2, or B6D2F1 mice (age, 5 weeks) were initiated with a single intraperitoneal dose of *N*-nitrosodiethylamine (NDEA) at 0 or 90 mg/kg bw, in tricaprylin. Three weeks later, the mice were placed on a diet containing Aroclor 1254 at a concentration of 100 ppm or the control diet for 20 weeks. After the promotion phase, the mice were left untreated until the terminal kill at age 52 weeks. Aroclor 1254 alone did not increase the incidence of tumours of the lung or liver in any of the three strains compared with their respective controls (Beebe *et al.*, 1995).

Four groups of 50 male BALB/cJ inbred mice (age, 5–6 weeks) were fed diets containing Aroclor 1254 (mixed with corn starch) at a concentration of 0 (control) or 300 ppm for up to 11 months (Kimbrough & Linder, 1974; Faroon *et al.*, 2001). After 6 months of exposure, one group of treated mice was fed the standard diet,

Table 3.5 Doses of PCB-118 and PCB-126 given to rats in a study of carcinogenicity by the NTP (2006d)

Dose (ng TEQ/kg bw)	Contribution to dose by mass[b]				Contribution to dose by TEQ[c] (ng TEQ/kg bw)				Total nominal dose by TEQ[c] (ng TEQ/kg bw)
	PCB-118 (µg/kg bw)	PCB-126 (ng/kg bw)	PCB-77[a] (ng/kg bw)	PCB-167[a] (ng/kg bw)	PCB-118	PCB-126	PCB-77[a]	PCB-167[a]	
7	10[d]	62	20	50	1.0	6.2	0.002	0.0005	7.2
22	30[d]	187	60	150	3.0	18.7	0.006	0.0015	21.6
72	100[d]	622	200	500	9.9	62.2	0.02	0.005	72.1
216	300[d]	1866	600	1500	29.6	186.6	0.06	0.015	216.2
360	500[d]	3110	1000	2500	49.3	311.0	0.1	0.025	360.4

[a] Present as contaminants that were not considered to contribute to the dioxin-like activity of the bulk synthesized test article
[b] Based on the level of each compound present in the bulk synthesized test article
[c] Assuming WHO TEF (toxic equivalency factor) values of 0.1 (PCB-126), 0.0001 (PCB-118), 0.0001 (PCB-77) and 0.00001 (PCB-167). TEQ value for PCB-118 was calculated assuming 98.5% of bulk material is PCB-118
[d] Nominal dose (µg/kg bw) of bulk synthesized material
PCB, polychlorinated biphenyl; TEQ, toxic equivalent

while the other treated group was fed the experimental diet for an additional 5 months; the two control groups were fed plain chow for an additional 5 months. Only one of 24 surviving mice given Aroclor 1254 for 6 months had a hepatoma [histopathology not further specified], while the incidence of hepatoma in the 22 surviving mice fed Aroclor 1254 for 11 months was significantly increased (10 out of 22; $P < 0.001$). Hepatomas were not found in any of the mice in the control groups.

(ii) Rat

Groups of 24 male and 24 female F344 rats (age, 7 weeks) were fed diets containing Aroclor 1254 at a concentration of 0, 25, 50, or 100 ppm in corn oil for up to 105 weeks (NTP, 1978; Ward, 1985; Safe, 1989; Silberhorn *et al.*, 1990; Faroon *et al.*, 2001). In males, hepatocellular adenoma was observed in one, two, and five of the rats at the lowest, intermediate, and highest dose, respectively, and hepatocellular carcinoma was observed in two rats at the highest dose; the incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) in males at the highest dose were statistically significantly increased. Hepatocellular tumours were not observed in controls. Non-statistically significant low incidences of rare adenocarcinomas of the glandular stomach were observed in both sexes. Adenocarcinoma of the glandular stomach was not observed in controls. The historical incidence of adenocarcinoma of the glandular stomach at the study laboratory (6 out of 600 males [1%], 2 out of 600 females [0.3%]) suggested that the occurrence of these tumours, although not statistically significant, may have been related to the administration of Aroclor 1254. There was a statistically significant dose-related trend in the combined incidences of lymphoma and leukaemia in male rats, but incidence in each dose group was not statistically significantly different from that in matched controls. Morgan *et al.* (1981) and Ward (1985) re-examined the gastrointestinal lesions observed in the study by the NTP (1978) and found a dose-related increase in the incidence of metaplasia of the glandular stomach, and also found adenocarcinoma of the glandular stomach in six treated rats. When compared with the incidence of adenocarcinoma of the glandular stomach in historical controls (1 out of 3548), the total incidence (6 out of 144 male and female rats treated with Aroclor 1254) was statistically significant.

(b) Aroclor 1260

Rat

Groups of 200 female Sherman rats (age, 21–26 days) were fed diets containing Aroclor 1260 at a concentration of 0 (control) or 100 ppm for approximately 21 months (Kimbrough *et al.*, 1975). The rats were killed at age 23 months. There were statistically significant increases in the incidences of "hepatic neoplastic nodules" and of hepatocellular carcinoma in rats receiving Aroclor 1260 compared with controls. The hepatocellular tumours were re-evaluated histologically by a panel of pathologists using contemporary diagnostic criteria and nomenclature (Moore *et al.*, 1994). Lesions that had been previously diagnosed as "neoplastic nodules" were reclassified as either hepatocellular hyperplasia or hepatocellular adenoma. In general, the results of the re-evaluation were consistent with those of the original evaluation.

Groups of 32 male Wistar rats (age, 5 weeks) were fed a 10% protein diet containing Aroclor 1260 (dissolved in coconut oil) at a concentration of 0 (control), 50, or 100 ppm for 120 days (Rao & Banerji, 1988; Silberhorn *et al.*, 1990). Controls were fed diet mixed with coconut oil. The incidences of "liver neoplastic nodules" [liver tumours] were significantly increased in both groups of treated rats; however, the incidence of tumours in rats fed the higher dose was lower than that in rats fed the lower dose.

Groups of 70 male and 70 female Sprague-Dawley rats were fed a diet containing Aroclor 1260 at a concentration of 100 ppm for 16 months, followed by diet containing Aroclor 1260 at 50 ppm for an additional 8 months, and then basal diet for 5 months (Norback & Weltman, 1985; Safe, 1989; Silberhorn *et al.*, 1990; Moore *et al.*, 1994; Faroon *et al.*, 2001). Groups of 63 males and 63 females served as controls and received the basal diet supplemented with corn oil for 18 months, and then the basal diet only for the remainder of the study. The medial and left lobes of the liver of 10 rats (two male controls, two female controls, three PCB-treated males and three PCB-treated females, for each time-point) were removed at 1, 3, 6, 9, 12, 15, and 18 months. In treated rats that survived 18 months or longer, malignant hepatic tumours (adenocarcinoma and/or trabecular carcinoma) were found in 43 out of 47 females, but only in 2 out of 46 males. The individual incidences of adenocarcinoma and of trabecular carcinoma in PCB-treated females were significantly greater than in controls. Hepatic neoplastic nodules [benign hepatocellular tumours] occurred in 5 out of 46 males, and 2 out of 47 females. A single hepatic neoplastic nodule occurred in a female control rat. PCB-exposed rats developed cystic cholangioma in 2 out of 46 males, and 5 out of 47 females [non-significant], versus 0 out of 32 males and 1 out of 49 females among the controls. Preneoplastic lesions of the biliary tract, referred to as simple and cystic cholangioma, also occurred at a higher incidence in treated males and females (30% and 45%, respectively).

(c) Aroclor 1016, 1242, 1254, and 1260

Rat

A comprehensive comparative long-term study of toxicity and carcinogenicity was conducted with four of the most widely used commercial Aroclor mixtures: Aroclor 1016, 1242, 1254, and 1260 (Mayes *et al.*, 1998; Faroon *et al.*, 2001; Brown *et al.*, 2007). Groups of 50 male and 50 female Sprague–Dawley rats (age, 6–8 weeks) were fed diets containing Aroclor 1016, 1242, 1254, or 1260 at doses ranging from 25 to 200 ppm (three dose levels for Aroclor 1016, 1254 and 1260, and two dose levels for Aroclor 1242) for 24 months. Groups of 100 males and 100 females served as controls. Aroclor 1016, 1242, 1254, and 1260 contained polychlorinated dibenzodioxins (PCDDs) at concentrations of 0.6, 0, 20, and 0 ppb, respectively, and polychlorinated dibenzofurans (PCDFs) at concentrations

of 0.035, 2.9, 23, and 4.9 ppm, respectively. The basal diet contained PCBs at less than 0.15 ppm (estimated dose, < 0.01 mg/kg bw per day). Aroclor 1254 was treated to remove > 99% of the PCDFs. Feeding with diets containing Aroclor led to increased incidences of hepatic neoplasms (primarily hepatocellular adenoma) that were highly sex-dependent (females > males) and that differed between Aroclor mixtures. For females, the incidences of hepatocellular adenoma and of hepatocellular carcinoma increased with dose, with the following pattern: Aroclor 1254 > Aroclor 1260 > Aroclor 1242 > Aroclor 1016. The number of females bearing multiple hepatocellular tumours also increased in a dose-related manner for all Aroclor mixtures, and the highest numbers were in the groups receiving the intermediate and highest dose of Aroclor 1254, and the highest dose of Aroclor 1260. In addition, in females receiving Aroclor 1260, there was an increase in the incidence of cholangioma. In males, an increased incidence of hepatocellular adenoma was observed only in the group receiving Aroclor 1260 at the highest dose. The incidence of follicular cell adenoma of the thyroid gland was significantly increased in males in a non-dose-dependent manner; these increases were induced by Aroclor 1242 (both doses), Aroclor 1254 (all doses), and Aroclor 1260 (lowest and intermediate doses).

(d) Kanechlor 300, 400, and 500

(i) Mouse

Groups of 20 male and 20 female dd strain albino mice [age not reported] were given diets containing one of three PCB mixtures (Kanechlor 300, 400, or 500) at a concentration of 0, 100, 250, or 500 ppm for 24 or 32 weeks (Nagasaki *et al.*, 1975). The incidence of hepatocellular carcinoma was significantly increased in male and female mice given Kanechlor 500 at 500 ppm for 32 weeks. No tumours of the liver were found in mice fed Kanechlor 500 at dietary concentrations of 100 or 250 ppm, or the lesser chlorinated commercial mixtures Kanechlor 400 or Kanechlor 300 at any of the three dietary concentrations at 24 or 32 weeks.

Groups of 12 male dd strain albino mice (age, 8 weeks) were fed basal diets supplemented with one of three PCB mixtures (Kanechlor 300, 400, or 500) at a concentration of 100, 250, or 500 ppm for 32 weeks; a control group of six mice was fed basal diet alone (Ito *et al.*, 1973; Silberhorn *et al.*, 1990; Faroon *et al.*, 2001). The incidences of hepatocellular carcinoma (5 out of 12 [not significant]) and liver hyperplastic nodules [some of which may have been hepatocellular adenomas] (7 out of 12 [$P < 0.05$]) were increased in mice fed diets containing Kanechlor 500 at 500 ppm compared with controls (0 out of 6). Hepatic lesions were not found in mice fed Kanechlor 500 at lower doses, or in mice exposed to the less chlorinated mixtures Kanechlor 400 or Kanechlor 300 for 32 weeks. Other histopathological changes in mice treated with PCBs included oval-cell proliferation, bile duct proliferation, hepatocyte hypertrophy, and amyloidosis. [The Working Group noted that the study may have been limited by the small number of mice, the relatively short treatment period, and the absence of an observation period after treatment.]

(ii) Rat

A group of 10 male and 10 female Donryu rats (age, 10 weeks) were fed diet containing Kaneclor 400 at a concentration of 38.5 ppm for 4 weeks, then the initial concentration was increased (based on body weights) twice for 8 weeks, 4 times for 3 weeks, 8 times for 3 weeks, and 16 times for 8 weeks (Kimura & Baba, 1973; Silberhorn *et al.*, 1990). The latter concentration was decreased to 12 times for 32 weeks because body weights were decreasing markedly. Rats were then fed basal diet until moribund, up to 560 days. A group of five males and five females fed basal diets served as controls. Treatment with Kanechlor 400 (duration, 400 days) caused

a significant increase in the incidence of multiple adenomatous nodules [hepatocellular adenoma] in females. None of the treated males developed adenomatous nodules. [The Working Group noted that the study may have been limited by the small numbers of animals, and may have exceeded the maximum tolerated dose.]

(e) Clophen A 30 and Clophen A 60

Rat

Male weanling Wistar rats were fed a diet supplemented with Clophen A 30 (42% chlorine by weight) or Clophen A 60 (60% chlorine by weight) at a concentration of 100 ppm, or an estimated dose of 5 mg/kg bw per day, for up to 832 days; controls were fed the basal diet (Schaeffer *et al.*, 1984; Young, 1985; Safe, 1989). Tumour incidence was investigated at intervals of 100 days. After 800 days, the overall incidence of hepatocellular neoplastic nodules, irrespective of time period, was significantly increased in rats fed Clophen A 30 (38 out of 130) or Clophen A 60 (63 out of 126) compared with controls (5 out of 131). The incidence of hepatocellular carcinoma was significantly increased in rats fed Clophen A 60 (61 out of 126 compared with 1 out of 131 controls). The incidences of hepatocellular lesions were re-evaluated by a panel of pathologists using contemporary diagnostic criteria and nomenclature (Moore *et al.*, 1994). Lesions that had been previously diagnosed as neoplastic nodules were now classified as either hepatocellular hyperplasia or hepatocellular adenoma. The results of the re-evaluation were generally consistent with those of the original evaluation.

3.2 Transplacental and perinatal exposure

This section covers those studies for which exposure to PCBs occurred either transplacentally and/or perinatally. This period generally covers exposure from day 1 of gestation until weaning on postnatal day 21, although it should be noted that weaning can occur at up to age 28 days.

3.2.1 Individual PCBs and binary mixtures

(a) PCB-126

See Table 3.6

Rat

Five groups of pregnant Sprague-Dawley rats were given PCB-126 at a dose of 0 (corn oil), 0.025, 2.5, 250, or 7500 ng/kg bw by gavage on days 13 to 19 of gestation. Female pups from the exposed dams were weaned on postnatal day 21, and subsequently exposed at age 50 days to 7,12-dimethylbenz[*a*]anthracene (DMBA) at a dose of 20 mg/kg bw in corn oil by gavage, and followed until age 170 days (Muto *et al.*, 2001). There was no specific perinatal oral exposure to PCB-126. There was a significant reduction in body weight in the groups of pups at 250 ng/kg bw and 7500 ng/kg bw at postnatal day 21, and at 7500 ng/kg bw at age 30 days. There was a significant reduction in the incidence of DMBA-induced tumours of the mammary gland in the group at 7500 ng/kg bw. In the group at 7500 ng/kg bw, 41% of tumours were adenomas, while tumours in all other groups were mainly adenocarcinomas. [The study design was not a full carcinogenesis bioassay of PCBs.]

In a similar study by Wakui *et al.* (2005), four groups of pregnant Sprague-Dawley rats were given PCB-126 at a dose of 0 (corn oil vehicle), 2.5, 250, or 7500 ng/kg bw by gavage on days 13 to 19 of gestation. Female pups from the exposed dams were weaned at postnatal day 21, and subsequently exposed at age 50 days to DMBA at a dose of 100 mg/kg bw in corn oil by gavage, and followed until age 150 days. As in the study by Muto *et al.* (2001), there was a significant reduction in the incidence of adenocarcinoma of the mammary gland in the group at 7500 ng/kg bw. [The study design was not a full carcinogenesis bioassay of PCBs.]

Table 3.6 Studies of carcinogenicity in rats exposed perinatally or transplacentally to PCB-126

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Sprague-Dawley (Japan SLC) (F) 170 day Muto *et al.* (2001)	Dams were treated with PCB-126 at 0 (corn oil vehicle), 0.025, 2.5, 250, or 7500 ng/kg bw (0.5 mL/rat) by gavage on days 13–19 of gestation. Pups were weaned at PND 21 Female pups (age 50 days) received DMBA at 20 mg/kg bw in corn oil by gavage and observed until age 170 days, or until tumours reached 20 mm in size Group 1: corn oil vehicle Group 2: 0.025 ng/kg bw Group 3: 2.5 ng/kg bw Group 4: 250 ng/kg bw Group 5: 7500 ng/kg bw 45/group	Tumours of the mammary gland: Group 1: 42/45, 3.12 ± 0.74 Group 2: 44/45, 2.77 ± 1.89 Group 3: 42/45, 3.98 ± 2.82 Group 4: 43/45, 5.09 ± 2.42 Group 5: 35/45*, 2.25 ± 1.55	*$P < 0.05$, χ^2 test (decrease)	Not a full carcinogenesis bioassay In the group at 7500 ng/kg bw, 41% of tumours were adenomas, whereas in all other groups the tumours were mainly adenocarcinomas
Sprague-Dawley (Japan SLC) (F) 150 day Wakui *et al.* (2005)	Dams were treated with PCB-126 at 0 (corn oil vehicle), 2.5, 250, 7500 ng/kg bw (0.5 mL/rat) by gavage on days 13–19 of gestation. Pups were weaned at PND 21 Females (age 50 days) received DMBA at 100 mg/kg bw in corn oil by gavage, and were observed until age 150 days Group 1: corn oil vehicle Group 2: 2.5 ng/kg bw Group 3: 250 ng/kg bw Group 4: 7500 ng/kg bw 25/group	Mammary gland, adenocarcinoma: Group 1: 22/25 (88%) Group 2: 21/25 (84%) Group 3: 23/25 (92%) Group 4: 16/25 (64%)*	*$P < 0.05$, χ^2 test (decrease)	Not a full carcinogenicity bioassay

DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; M, male; NDMA, *N*-nitrosodimethylamine; PND, postnatal day; wk, week

(b) PCB-153 and PCB-138

See Table 3.7

Mouse

Eight groups of male Swiss Cr:NIH(s) mice were given an intraperitoneal injection of *N*-nitrosodimethylamine (NDMA) at 0 (saline vehicle) or 5 mg/kg bw on postnatal day 4. On postnatal day 8, the mice were treated by gavage with PCB-153 or PCB-138, or a mixture of the two PCBs, each at a single dose of 20 mg/kg bw, or with the vehicle, olive oil (Anderson *et al.*, 1991). The concentration selected, 20 mg/kg bw, is approximately equivalent to the concentration of each PCB congener in a dose of 500 mg/kg bw of Aroclor 1254. The mice were killed at age 16 weeks. There was no effect of either PCB congener alone or in combination on the incidence of bronchioloalveolar adenoma in the absence of treatment with NDMA. In NDMA-initiated mice, there was a significant increase in the multiplicity of bronchioloalveolar adenoma in mice also exposed to PCB-138. There was no effect of PCB-153, or of PCB-153 plus PCB-138, when compared with controls treated with NDMA only. [This study was not a full carcinogenesis bioassay. It was limited regarding the effect of the PCBs alone without initiation, due to the short duration of observation.]

3.2.2 Commercial mixtures of PCBs

(a) Aroclor 1254

See Table 3.8

Mouse

Pregnant CD-1 mice were given a single intraperitoneal injection of Aroclor 1254 at a dose of 0 (corn oil) or 500 mg/kg bw on day 19 of gestation (Anderson *et al.*, 1983). Suckling mice were given NDMA at 0 (saline vehicle) or 5 mg/kg bw by intraperitoneal injection on postnatal day 4 or 14, or every 3 days on postnatal days 1–22. Mice were weaned at age 4 weeks and examined at approximately 28 weeks and 18 months. No tumours of the liver were found at 28 weeks in male or female mice exposed in utero to the vehicle or Aroclor 1254 alone without exposure to NDMA. At 18 months, there was no increase in the incidence of tumours of the liver in mice treated with Aroclor 1254 without NDMA exposure. In the groups that were exposed to NDMA on postnatal day 4 or 14, there was no effect of maternal exposure to Aroclor 1254 on the incidence or multiplicity of tumours of the liver in male or female mice. Nevertheless, at 18 months, there was a significant increase in the incidence of "coalescing" tumours of the liver in females exposed on postnatal day 4 and in males exposed on postnatal day 14. There was no effect of maternal exposure to Aroclor 1254 on the incidence or multiplicity of tumours of the liver in male or female pups treated with NDMA between postnatal days 1 and 22. [This study design was not a full carcinogenesis bioassay of PCBs. Although mice were exposed to PCBs before being exposed to NDMA, NDMA acts as an initiator. Thus results from the groups exposed to NDMA plus PCBs are more likely to reflect an effect of the exposure to PCBs in utero on NDMA carcinogenesis.]

Groups of male neonatal Swiss Cr:NIH(s) mice were injected intraperitoneally with NDMA at a dose of 5 mg/kg bw in saline on postnatal day 4 (Anderson *et al.*, 1986). On postnatal day 8, mice were exposed to Aroclor 1254 at a dose of 0 (control), 50, 250, or 500 mg/kg bw in olive oil by gavage, for 16 or 28 weeks. The study also included two non-initiated groups exposed to Aroclor 1254 at a dose of 0 or 500 mg/kg bw. A significant increase in the average number of bronchioloalveolar adenomas was observed in mice exposed to both NDMA and Aroclor 1254 compared with mice exposed to NDMA only, but not in mice exposed to Aroclor 1254 without NDMA initiation compared with mice exposed to vehicle only.

Table 3.7 Study of carcinogenicity in mice exposed perinatally to PCB-153 and PCB-138

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Swiss Cr:NIH(s) (M) 16 wk Anderson *et al.* (1991)	Intraperitoneal injection on PND 4 with NDMA at 5 mg/kg bw or saline vehicle Exposure on PND 8 to PCBs (in olive oil) at 20 mg/kg bw by gavage until age 16 wk Group 1: NDMA Group 5: NDMA + PCB-153 Group 6: NDMA + PCB-138 Group 7: NDMA + PCB-153 + PCB-138 Group 8: saline/olive oil Group 2: PCB-153 Group 3: PCB-138 Group 4: PCB-153 + PCB-138 Number/group, NR	Bronchioloalveolar adenoma: Group 1: 15/55 (27%), 0.42 ± 0.11 Group 5: 13/53 (24%), 0.3 ± 0.08 Group 6: 21/50 (42%), 1.0 ± 0.3* Group 7: 14/46 (30%), 0.52 ± 0.13 Group 8: 0/26 Group 2: 0/32 Group 3: 0/31 Group 4: 0/34	*P = 0.014 vs group 1	Purity, NR Not a full carcinogenicity bioassay Concentration of PCBs (20 mg/kg bw) is approximately equivalent to that of each PCB congener in Aroclor 1254 at 500 mg/kg bw

M, male; NDMA, *N*-nitrosodimethylamine; PCB, polychlorinated biphenyl; PND, postnatal day; vs, versus

Table 3.8 Studies of carcinogenicity in mice exposed perinatally or transplacentally to Aroclor 1254

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
CD-1 (M, F) 28 wk and 18 mo Anderson *et al.* (1983)	Pregnant dams given a single intraperitoneal injection of Aroclor 1254 at 0 (olive oil vehicle) or 500 mg/kg bw on day 19 of gestation. Progeny then injected intraperitoneally with saline (experiment 1) or NDMA at 5 mg/kg bw on PND 4 (experiment 2), PND 14 (experiment 3), or every 3 days from PND 1 to 22 (experiment 4) Group 1: olive oil (F, 28 wk) Group 2: Aroclor 1254 (F, 28 wk) Group 3: olive oil (F, 18 mo) Group 4: Aroclor 1254 (F, 18 mo) Group 5: olive oil (M, 28 wk) Group 6: Aroclor 1254 (M, 28 wk) Group 7: olive oil (M, 18 mo) Group 8: Aroclor 1254 (M, 18 mo) Number of mice/group, NR	*Experiment 1 (no NDMA):* Liver tumours: 0/23, 0/21, 1/31, 1/23, 0/21, 0/23, 12/23, 8/25 *Experiment 2 (NDMA on PND 4):* Liver tumours: 3/17, 3/21, 21/29, 17/20, 17/23, 14/24, 27/28, 17/17 Liver (coalescing) tumours: 0/17, 0/21, 7/29, 13/20*, 17/23, 14/24, 27/28, 17/17 *Experiment 3 (NDMA on PND 14):* Liver tumours: 2/18, 0/19, 16/24, 9/19, 9/26, 1/19**, 18/19, 18/19 Liver (coalescing) tumours: 0/18, 0/19, 3/24, 1/19, 0/26, 0/19, 8/19, 14/19***	NS NS *$P < 0.01$ (Fisher exact test) **$P < 0.04$ (Fisher exact test), decrease ***$P < 0.035$ (Fisher exact test)	Purity, NR Tumour incidence and multiplicity in progeny (from dams treated with Aroclor 1254) exposed to NDMA every 3 days from PND 1 to PND 22 (experiment 4) were not increased and are not shown
Swiss Cr:NIH(s) (M) 16 or 28 wk Anderson *et al.* (1986)	Intraperitoneal injection of NDMA (0 or 5 mg/kg bw) in saline on PND 4 followed on PND 8 by exposure to Aroclor 1254 in olive oil by gavage Groups were exposed for 16 or 28 wk to: NDMA + Aroclor 1254 (50 mg/kg bw); NDMA + Aroclor 1254 (250 mg/kg bw); NDMA + Aroclor 1254 (500 mg/kg bw); NDMA + olive oil; saline + Aroclor 1254 (500 mg/kg bw); saline + olive oil Number/group, NR	Bronchioloalveolar adenoma (average no. of tumours/no. of examined animals): 16 wk: 5.7/16, 5.1/12, 11.8/14*, 6.1/17, 0/13, 0.2/6 28 wk: 7.9/15, 8.6/14, 11.9/16**, 6.6/16, 0.2/19, 0.1/7	*$P < 0.05$ **$P < 0.01$	Purity, NR Not a full carcinogenicity bioassay. Short duration

Table 3.8 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Swiss Cr:NIH(s) (M) up to 72 wk Anderson *et al.* (1994)	Intraperitoneal injection on PND 4 with NDMA at 5 mg/kg bw or saline vehicle. At age 8 days, mice received Aroclor 1254 at 250 mg/kg bw by gavage in olive oil or vehicle only. Mice were killed when moribund or at age 16, 28, 52, or 72 wk Groups were exposed to: NDMA; NDMA + Aroclor 1254; Aroclor 1254; saline/oil Number/group, NR	*Bronchioloalveolar adenoma:* Age 28 wk: 7/23[a] (30%), 0.5 ± 1.1[b]; 19/27[a] (70%), 1.9 ± 2.9[b]; 0/13; 0/16 Age 52 wk: 12/25 (48%), 0.6 ± 0.8[c]; 15/23 (65%), 2.7 ± 3.8[c]; 4/24 (17%), 0.17 ± 0.38; 6/27 (22%), 0.26 ± 0.4 Age 72 wk: 21/23 (91%), 5.1 ± 4.5; 17/23 (74%), 3.9 ± 4.3; 17/25 (68%), 0.9 ± 0.8; 17/39 (44%), 0.6 ± 0.7 *Liver adenoma:* Age 52 wk: 1/25[d] (4%), 0.04 ± 0.2; 9/23[d] (39%), 0.6 ± 0.8; 0/24; 0/27 Age 72 wk: 16/23 (70%), 1.8 ± 2.2; 14/25 (56%), 1.5 ± 2.0; 0/25; 0/39	Matched letters are significantly different from each other [a]$P = 0.01$ [b]$P = 0.0033$ [c]$P = 0.0496$ [d]$P = 0.004$	Purity, NR Not a full carcinogenicity bioassay

mo, month; NDMA, *N*-nitrosodimethylamine; NR, not reported; NS, not significant; PND, postnatal day; wk, week

In a subsequent experiment, groups of neonatal male Swiss Cr:NIH(s) mice were given an intraperitoneal injection of NDMA at a dose of 0 (saline vehicle) or 5 mg/kg bw on postnatal day 4, then given Aroclor 1254 at a dose of 0 or 250 mg/kg bw in olive oil on day 8 by gavage, and killed at age 16, 28, 52, or 72 weeks (Anderson *et al.*, 1994). At age 28 weeks, the incidence of bronchioloalveolar adenoma in mice initiated with NDMA was increased 2.5-fold by treatment with Aroclor 1254. The multiplicity of bronchioloalveolar adenoma was enhanced fourfold by treatment with Aroclor 1254 for 28 or 52 weeks. By 72 weeks, tumour numbers, although high, were similar in the groups receiving NDMA only, and NDMA plus Aroclor 1254. There was an increased incidence of liver adenoma at 52 weeks in mice receiving NDMA plus Aroclor 1254 compared with mice receiving NDMA only. By 72 weeks, the incidences in the groups receiving NDMA or NDMA plus Arochlor 1254 were similar. [This study was not a full carcinogenesis bioassay of PCBs.]

(b) Kanechlor 500

See Table 3.9

Rat

Pregnant Wistar rats were exposed to Kanechlor 500 at a dose of 0 (olive oil vehicle), 40, or 200 mg/kg bw by gavage on days 5, 10, and 15 of gestation (Nishizumi, 1980). Male and female pups were subsequently weaned and given drinking-water containing NDEA at 50 ppm for 5 weeks to induce liver tumours [mainly hepatocellular carcinomas] that were evaluated after 20 and 24 weeks. The average concentration of total PCBs in the liver at 4 weeks was 1 ppm, 18 ppm and 360 ppm in the groups at 0 (vehicle), 40 mg/kg bw and 200 mg/kg bw, respectively, indicating clear transfer from the dam to the offspring. In both males and females, there was a decrease in the multiplicity of NDEA-initiated tumours of the liver. [This study was not a full carcinogenesis bioassay.]

3.2.3 Mixtures of PCBs and other chlorinated agents found in human milk fat

*(a) Mixture of non-*ortho *PCBs, PCDFs, and PCDDs*

See Table 3.10

Rat

Female Sprague-Dawley rats were exposed by gavage at age 1, 5, 10, 15, and 20 days to a mixture of three non-*ortho* PCBs [PCB-77, PCB-126, and PCB-169], six PCDDs, and seven PCDFs, or were exposed to the vehicle (corn oil) only (Desaulniers *et al.*, 2004). The concentrations of these agents in the mixture were based on the concentrations of dioxin-like congeners found in human milk fat, and the doses administered were equal to 10 times, 100 times, or 1000 times the quantities found in milk fat. At age 50 days, groups of rats were injected intraperitoneally with *N*-methyl-*N*-nitrosourea (MNU) at a dose of 0 or 30 mg/kg bw to induce the development of tumours of the mammary gland. At age 32 weeks, in those groups not treated with MNU, there was a significant increase in the incidence of benign lesions of the mammary gland (adenoma, fibroadenoma, and hyperplasia) after exposure to the 1000-times mixture. In the MNU-treated groups, there was no effect of exposure to the mixture on the incidences of benign lesions or malignant tumours of the mammary gland. [This study was not a full carcinogenesis bioassay. Given the presence of PCDDs and PCDFs in the mixture, conclusions regarding the effect of PCBs alone could not be drawn from this study.]

(b) Mixture of PCBs, DDT, and DDE

See Table 3.11

Rat

Neonatal female Sprague Dawley rats were exposed to a mixture of 19 PCB-congeners, *p,p´*-dichlorodiphenyltrichloroethane (DDT), and *p,p´*-dichlorodiphenyldichloroethene (DDE)

Table 3.9 Study of carcinogenicity in rats exposed transplacentally and perinatally to Kanechlor 500

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), multiplicity of tumours	Significance	Comments
Wistar (M, F) up to 29 wk Nishizumi (1980)	Dams were given Kanechlor 500 at 0 (olive oil vehicle), 40, or 200 mg/kg bw by gavage on days 5, 10 and 15 of gestation. Male and female offspring were given drinking-water containing NDEA at 50 ppm for 5 wk, and were evaluated 20 and 24 wk after NDEA exposure Group 1: vehicle (olive oil) Group 2: Kanechlor 500 at 40 mg/kg bw Group 3: Kanechlor 500 at 200 mg/kg bw 6–8 M and 6–8 F/group	Liver tumours (≥ 5 mm) *M (20 wk):* Group 1: 6/7 (86%), 3.0 ± 0.7 Group 2: 6/8 (75%), 1.3 ± 0.4* Group 3: 4/6 (50%), 1.0 ± 0.4* *F (20 wk):* Group 1: 5/8 (62.5%), 1.1 ± 0.4 Group 2: 4/8 (50%), 0.6 ± 0.3 Group 3: 0/8, 0* *M (24 wk):* Group 1: 8/8 (100%), 4.6 ± 0.7 Group 2: 6/6 (100%), 2.8 ± 0.7 Group 3: 5/7 (71%), 2.0 ± 0.7* *F (24 wk):* Group 1: 4/7 (57%), 1.4 ± 0.5 Group 2: 3/7 (43%), 0.7 ± 0.4 Group 3: 2/8 (25%), 0.4 ± 0.3	*$P < 0.05$ (decrease)	Not a full carcinogenesis bioassay Liver tumours were mainly hepatocellular carcinomas, with some neoplastic nodules

F, female; M, male; NDEA, *N*-nitrosodiethylamine; wk, week

Table 3.10 Studies of carcinogenicity in rats exposed perinatally to a mixture of non-*ortho* PCBs, PCDDs, and PCDFs

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: Incidence of tumours	Significance	Comments
Sprague-Dawley Charles River, St-Constant, QC (F) 32 wk Desaulniers *et al.* (2004)	Mixture (5 mL/kg bw) in corn oil given to neonates at age 1, 5, 10, 15, and 20 days, by gavage. Mixture contained 0 (vehicle), 1, 10, 100, or 1000 times the amount a human baby would consume. MNU was injected intraperitoneally (30 mg/kg bw in saline) at age 50 days. The rats were killed at age 32 wk	*Mammary gland:*		Purity, NR Short duration; not a full carcinogenicity bioassay The concentrations of each chemical included in the mixture (three non-*ortho* PCBs [PCB-77, PCB-126, and PCB-169], six PCDDs and seven PCDFs) were based on the concentrations found in human milk fat Description of benign lesions of the mammary gland did not differentiate between non-neoplastic (hyperplasia) and neoplastic (adenoma, fibroadenoma) lesions Mixture included PCDDs and PCDFs, so conclusions could not be made regarding the effect of PCBs alone
	Without MNU: vehicle (controls), 1000× mixture	Benign lesions (adenoma, fibroadenoma, hyperplasia): 4/37, 11/37* Malignant (carcinoma in situ and adenocarcinoma): 1/37, 4/37	* $P < 0.05$	
	With MNU: vehicle (controls), 1 × mixture, 10 × mixture, 100 × mixture, 1000 × mixture 31–40/group	Benign lesions: 11/35, 8/32, 14/32, 12/31, 10/40 Malignant tumours: 24/35, 18/32, 19/32, 21/31, 25/40	NS	

F, female; M, male; MNU, *N*-methyl-*N*-nitrosourea; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; wk, week

Table 3.11 Study of carcinogenicity in rats exposed perinatally to a mixture of PCBs, DDT, and DDE found in breast milk

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) of tumours	Significance	Comments
Sprague-Dawley (F) 308 days or when tumour size reached 1 cm Desaulniers *et al.* (2001)	Neonates treated by gavage at age 1, 5, 10, 15, and 20 days with a mixture[a] containing 0 (vehicle), 10, 100 or 1000 times the amount of PCBs, DDT, DDE that a human baby would consume. A separate group received TCDD at 2.5 µg/kg bw by gavage on day 18. On day 21, groups 3–7 received a single intraperitoneal injection of MNU at 30 mg/kg bw in saline Group 1: corn oil vehicle controls Group 2: 1000 × mixture Group 3: MNU + corn oil vehicle Group 4: MNU + 10 × mixture Group 5: MNU + 100 × mixture Group 6: MNU + 1000 × mixture Group 7: MNU + TCDD 33–41/group	*Mammary gland* Groups 1 and 2: Fibroadenoma: 1/30, 0/33 Adenoma: 0/30, 0/33 Papilloma: 0/30, 0/33 Carcinoma in situ: 0/30, 1/33 Adenocarcinoma: 0/30, 0/33 Benign or malignant lesions (combined): 1/30, 2/33 Groups 3–7: Fibroadenoma: 12/41, 13/28, 6/31, 9/34, 10/32 Adenoma: 5/41, 4/28, 4/31, 8/34, 6/32 Papilloma: 3/41, 1/28, 3/31, 1/34, 5/32 Carcinoma in situ: 5/41, 5/28, 8/31, 7/34, 4/32 Adenocarcinoma: 11/41, 12/28, 10/31, 12/34, 13/32 Benign or malignant lesions (combined): 28/41, 24/28, 22/31, 25/34, 25/34 Benign or malignant lesions (median number of lesions): 2, 2, 1, 4.5*, 5.5	Group 2 vs group 1: NS Groups 4–7 vs group 3: NS for incidence *P = 0.05	Purity, NR Mixture included DDT and DDE, so conclusions could not be made regarding the effect of PCBs alone Not a full carcinogenesis bioassay

[a] Mixture consists of *p,p´*-dichlorodiphenyltrichloroethane (DDT), *p,p´*-dichlorodiphenyldichloroethene (DDE) and PCBs mixture comprised of non-*ortho* (PCB-77, -126, -169), mono-*ortho* (PCB-28, -66, -74, -118, -156) and di-*ortho* (PCB-99, -128, -138, -153, -170, -180, -183, -187, -194, -201, -203) substituted congeners detected in > 75% of breast milk samples from Canadian women. DDT, DDE and PCBs were included in the mixture according to the median concentrations in milk fat

MNU, *N*-methyl-*N*-nitrosourea; NS, not significant; PCB, polychlorinated biphenyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; vs, versus

(Desaulniers *et al.*, 2001). The PCB-congeners in the mixture were those detected in more than 75% of samples of breast milk from Canadian women and were included in proportions determined by their median concentrations measured in milk fat. The PCBs were: non-*ortho* (PCB-77, PCB-126, PCB-169), mono-*ortho* (PCB-28, PCB-66, PCB-74, PCB-118, PCB-156), and di-*ortho* (PCB-99, PCB-128, PCB-138, PCB-153, PCB-170, PCB-180, PCB-183, PCB-187, PCB-194, PCB-201, PCB-203) substituted congeners. In this study, five groups of neonatal rats were exposed to the mixture composed of DDT, its major metabolite DDE, and PCBs at 0 (corn oil), 10, 100, or 1000 times their concentrations in breast milk, by gavage, starting at age 1, 5, 10, 15, or 20 days. For comparison purposes, an additional group was exposed by gavage at age 18 days to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) at a concentration of 2.5 µg/kg bw. On day 21, all treatment groups (except for a control group that received corn oil only, and a group that received the 1000-times mixture) received a single intraperitoneal injection of MNU (30 mg/kg bw) in saline. Animals were observed up to 308 days. Seven to nine rats from the groups not exposed to MNU were killed between ages 55 and 62 days; the remaining rats were killed at 224 days. MNU-treated rats were killed when palpable tumours reached 1 cm, or by day 308 if no palpable tumour was detected. Sporadic incidences of lesions of the mammary gland were observed in the groups not treated with MNU (0 and 1000-times mixture). On the contrary, a large number of lesions of the mammary gland (including hyperplasia, the most common lesion observed) were seen in MNU-treated rats, and there was a significant effect of the 1000-times mixture ($P = 0.05$) on the median number of combined benign and malignant lesions of the mammary gland when compared to the MNU-only treated rats. There was no significant effect on the incidence of any specific tumour type, either benign or malignant, or the combined incidence of benign and malignant neoplasms. [Given that the mixture contained DDT and DDE, in addition to PCBs, the Working Group considered this study as a co-carcinogenicity study, and conclusions regarding the effect of PCBs alone could not be made.]

3.2.7 PCB metabolites: 4′-OH-PCB-30 and 4′-OH-PCB-61

See Table 3.12

Mouse

Neonatal female BALB/cCrg1 mice were exposed 16 hours after birth onwards to: 20 or 200 µg of 2′,4′,6′-trichloro-4-biphenylol [4′-OH-PCB-30]; 40 or 400 µg of 2′,3′,4′,5′-tetrachloro-4-biphenylol [4′-OH-PCB-61]; 10 µg of 4′-OH-PCB-30 plus 10 µg of 4′-OH-PCB-61, or 100 µg of 4′-OH-PCB-30 plus 100 µg of 4′-OH-PCB-61 (Martinez *et al.*, 2005). Exposure occurred via daily subcutaneous injections for 5 days and the mice were held for 20 months. [The neonatal mouse model has previously been used as a model for diethylstilbestrol-induced carcinogenesis after exposure in utero. The BALB/c mouse is known to be sensitive to the induction of cervicovaginal tumours by estrogens.] Significant treatment-related increases in the incidence of cervicovaginal tumours were observed for the groups treated with 4′-OH-PCB-30. Modest but statistically significant increases in the incidence of cervicovaginal tumours were also seen in both groups exposed to 4′-OH-PCB-61, and to the combination of 4′-OH-PCB-30 + 4′-OH-PCB-61 at the higher dose. There was also a significant effect of 4′-OH-PCB-61 at the lower dose on the incidence of carcinoma of the mammary gland.

Table 3.12 Study of carcinogenicity in mice exposed perinatally to 2′,4′,6′-trichloro-4-biphenylol (OH-PCB-30) and/or 2′,3′,4′,5′-tetrachloro-4-biphenylol (4′-OH-PCB-61)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence of tumours	Significance	Comments
BALB/cCrgl (F) Up to 20 mo Martinez *et al.* (2005)	Daily subcutaneous injections of 20 µL for 5 days starting 16 hours after birth. Mice were weaned at age 21 days. Examination daily for premature vaginal opening for the first 35 days of life and checks monthly to detect concretions. When concretions were found, the mice were removed from the study. All mice that survived to age 20 mo were killed Groups were injected with: sesame oil vehicle (control); 20 µg OH-PCB-30; 200 µg OH-PCB-30; 40 µg OH-PCB-61; 400 µg OH-PCB-61; 10 µg OH-PCB-30 + 10 µg OH-PCB-61; or 100 µg OH-PCB-30 + 100 µg OH-PCB-61 Number/group, NR	Cervicovaginal tract carcinoma: 0/33, 2/33, 10/22**, 4/30*, 5/24*, 3/36, 8/21* Mammary gland carcinoma: 0/33, 5/33, 0/22, 4/30*, 1/24, 3/36, 0/21	*$P < 0.05$ (Fisher exact test) **$P < 0.01$ (Fisher exact test)	Purity, NR The BALB/c mouse is sensitive to the induction of cervicovaginal tumours by estrogens. The inbred BALB/cCrgl strain has a low incidence of tumours of the mammary gland. The neonatal mouse model has previously been used as a model for diethylstilbestrol-induced carcinogenesis after exposure in utero Carcinomas of the cervicovaginal tract were mainly squamous cell carcinomas and adenosquamous carcinomas

F, female; mo, month; NR, not reported; PCB, polychlorinated biphenyl

3.3 Initiation–promotion and co-carcinogenicity studies

See Table 3.13

3.3.1 Initiation–promotion studies

(a) PCB-153

A study was carried out to determine whether PCB-153 had promoting activity in NDEA-initiated tumours of the liver in male B6129SF2/J mice, and whether the deletion of the NF-κB p50 subunit influenced liver carcinogenesis (Glauert *et al.*, 2008). Four groups of 14–17 wildtype and transgenic mice were injected intraperitoneally with NDEA (90 mg/kg bw in saline) at 9 weeks of age. After a 2-week recovery period, both wildtype and NF-κB $p50^{-/-}$ mice were injected intraperitoneally with PCB-153 at a dose of 0 (corn oil) or 300 µmol/kg bw every 14 days for a total of 20 injections. Mice were then maintained for an additional 15 weeks before being killed. Hepatocellular tumours were mainly classified as hepatocellular carcinoma. The incidence of hepatocellular tumours was higher in wildtype mice treated with PCB-153 than in wildtype mice receiving corn oil only. The deletion of p50 decreased the incidence of hepatocellular tumours in mice treated with PCB-153 or corn oil only.

(b) Aroclor 1254

(i) Mouse

In a study to determine whether Aroclor 1254 promoted the induction of liver nodules after initiation with NDEA, groups of male CD-1 mice were first given drinking-water containing NDEA at a dose of 0 or 8 µg/g bw per day, for 8 weeks (Gans & Pintauro, 1986). After 2.5 weeks, mice were given Aroclor 1254 as an intraperitoneal dose at 0 (tricaprylin/corn oil, 1/4, v/v) or 100 µg/g bw, every second week for 8 (8 mice per group) or 16 (18–19 mice per group) weeks. Aroclor 1254 did not increase the incidence of liver nodules, which were made up of type I, type II, or more commonly a mixture of type I and type II tissues. [The Working Group noted that it was not clear whether the diagnosis referred to hyperplasia and adenoma, respectively.]

Diwan *et al.* (1994) examined whether Aroclor 1254 promoted NDEA-initiated tumours of the liver in groups of 30 male DBA/2NCr × C57BL/6NCr (D2B6F1) mice. At age 5 weeks, mice were injected intraperitoneally with NDEA at a dose of 0 (tricaprylin vehicle) or 90 mg/kg bw. At age 7 weeks, mice were fed Aroclor 1254 at a dietary concentration of 175 or 350 mg/kg. The authors estimated the dose to be 0.1 or 0.2 mmol/kg bw per day based on a diet consumption of 4.5 g/day. [It was not reported whether food intake was measured.] Mice were killed after 60 weeks. The incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in both groups receiving NDEA plus Aroclor 1254 (all tumours were carcinomas) compared with the group receiving NDEA only (all tumours were adenomas). The incidences of hepatoblastoma in the group receiving Aroclor 1254 at 175 mg/kg, and of metaplastic and neoplastic glandular lesions within hepatocellular neoplasms (cholangiocellular neoplasms) in the groups receiving Aroclor 1254 at 175 and 350 mg/kg were higher [$P < 0.01$] than in the group receiving NDEA only.

Beebe *et al.* (1995) examined the promoting activity of Aroclor 1254 in the lung and liver in three strains of male mice that differ in AhR responsiveness: C57BL/6, DBA/2NCr, and B6D2F1. At age 5 weeks, groups of 23–34 mice were injected intraperitoneally with NDEA at a dose of 0 (tricaprylin vehicle) or 90 mg/kg bw. At age 8 weeks, the mice were placed on a diet containing Aroclor 1254 at a concentration of 0 or 100 mg/kg for 20 weeks. They were then left untreated for 24 weeks until being killed at age 52 weeks. Tumours of the liver were classified as hepatocellular adenoma, hepatocellular

Table 3.13 Initiation–promotion and co-carcinogenicity studies with PCBs

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Initiation–promotion studies (initiator followed by PCB)					
PCB-153	Mouse, wildtype (WT) and NF-κB p50$^{-/-}$ B6129SF2/J mice (M) 55 wk Glauert *et al.* (2008)	Initiation: NDEA (90 mg/kg, i.p.) at age 9 wk Promotion: 2 wk later, PCB-153 (300 µmol/kg bw in corn oil) by i.p. injection, every 14 days; total of 20 injections; then maintained for an additional 15 wk. 14–17/group	*Hepatocellular tumours* Corn oil controls: WT, 11/15 NF-κB p50$^{-/-}$, 5/11 PCB-153: WT, 7/7* NF-κB p50$^{-/-}$, 6/9	*[$P < 0.05$] vs WT mice receiving corn oil	Hepatocellular tumours were mainly carcinomas
Aroclor 1254	Mouse, CD-1 (M) 8 or 16 wk Gans & Pintauro (1986)	*Initiation:* NDEA, 0 (control) or 8 µg/g bw per day, in drinking-water, for 8 wk *Promotion:* 2.5 wk later, Aroclor 1254 at 100 µg/g bw in tricaprylin/corn oil vehicle, i.p. every other wk for 8 (8/group) or 16 wk (18–19/group)	Liver nodules of types I and II *8 wk:* Control + vehicle: 0/8 NDEA + vehicle: 2/8 Control + Aroclor 1254: 0/8 NDEA + Aroclor 1254: 2/8 *16 wk:* Control + vehicle: 0/18 NDEA + vehicle: 9/19 Control + Aroclor 1254: 1/18 NDEA + Aroclor 1254: 10/18	NS (effect of Aroclor 1254)	It was uncertain whether liver nodules included hyperplasias and adenomas Types not further identified
Aroclor 1254	Mouse, D2B6F1 (M) 60 wk Diwan *et al.* (1994)	*Initiation*: NDEA (0 or 90 mg/kg bw in saline, i.p.) at age 5 wk *Promotion*: Aroclor 1254 at 0, 175 or 350 mg/kg diet, at age 7 wk 30/group	*Hepatocellular adenoma or carcinoma (combined)* NDEA: 12/30 (3.4), 24/24* (10.8), 23/23* (16.9) Saline: 7/30 (1.1), 12/29 (2.1), 25/25 (2.9) *Hepatoblastoma* NDEA: 1/30 (1), 8/24* (1.5), 2/23 (1) Saline: NR, 0/29, 0/25 *Cholangiocellular tumours:* NDEA: 0/30, 7/24*, 17/23* Saline: NR, 2/29, 10/25	*$P < 0.00001$ *[$P < 0.01$] *[$P < 0.01$]	In both NDEA + Aroclor 1254 groups all tumours were carcinomas whereas in the NDEA-only group all tumours were adenomas

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254	Mouse, C57BL/6, DBA/2NCr, and B6D2F1 (M) 44 wk Beebe *et al.* (1995)	*Initiation*: NDEA (90 mg/kg bw, i.p.) or tricaprylin vehicle at age 5 wk *Promotion*: at age 8 wk, Aroclor 1254 (100 mg/kg diet) for 20 wk followed by no-exposure phase of 24 wk Group 1: Tricaprylin Group 2: NDEA Group 3: NDEA+Aroclor 1254 Group 4: Tricaprylin+Aroclor 1254 23–34/group	*C57BL/6* Liver tumours (all types): 0/27, 4/28, 19/32*, 2/27 Hepatocellular adenoma: 0/27, 4/28, 17/32**, 2/27 Hepatocellular carcinoma: 0/27, 3/28, 3/32, 0/27 Cholangioadenoma or cholangiocarcinoma (combined): 0/27, 0/28, 4/32, 0/27 Hepatoblastoma: 0/27, 0/28, 4/32, 0/27 Lung tumours (all): 1/27, 20/26, 20/25, 1/27 *B6D2F1* Liver tumours (all types): 0/34, 7/33, 8/33, 3/34 Hepatocellular adenoma: 0/34, 6/33, 6/33, 3/34 Hepatocellular carcinoma: 0/34, 0/33, 2/33, 0/34 Cholangioadenoma or cholangiocarcinoma (combined): 0/34, 0/33, 0/33, 0/34 Hepatoblastoma: 0/34, 1/33, 0/33, 0/34 Lung tumours (all): 0/31, 33/34, 31/34, 2/34	*$P < 0.05$ (group 3 vs group 2) **$P < 0.05$ (group 3 vs group 2 and group 3 vs group 4)	Purity, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254 (cont.)			*DBA/2* Liver tumours (all types): 0/23, 6/28, 6/31***, 0/24 Hepatocellular adenoma: 0/23, 5/28, 4/31, 0/24 Hepatocellular carcinoma: 0/23, 2/28, 2/31, 0/24 Cholangioadenoma or cholangiocarcinoma (combined): 0/23, 0/28, 0/31, 0/24 Hepatoblastoma: 0/23, 0/28, 0/31, 0/24 Lung tumours (all): 3/23, 24/28, 28/29, 1/24	***$P < 0.05$ (group 3 vs group 4)	
Aroclor 1254	Mouse, HRS/1 hairless (F) 20 wk Poland *et al.* (1982)	*Initiation*: MNNG (5 µmol in 50 µl of acetone) at age 8 wk *Promotion*: 1 mg Aroclor 1254 in 50 µL of acetone per mouse, twice weekly topically for 20 wk 20 mice in groups receiving Aroclor 1254; 26 in MNNG-only group	Skin papilloma: MNNG + vehicle, 0/23 Vehicle + Aroclor 1254, 0/19 MNNG + Aroclor 1254, 4/19	NS	Statistical test, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254	Mouse, Swiss (Cr:NIH) (M, F) 44 wk Beebe *et al.* (1993)	*Initiation:* For transplacental studies, pregnant mice were injected with NNK (100 mg/kg bw, i.p.) on days 15, 17, and 19 of gestation, or with NDMA (10 mg/kg bw, i.p.) on day 19 of gestation, or with saline vehicle on day 19 of gestation For neonatal studies, pups were injected with NDMA (5 mg/kg bw, i.p.), NNK (50 mg/kg bw, i.p.), or saline vehicle on PND 4 *Promotion:* Aroclor 1254 (500 mg/kg bw, p.o.) or olive oil vehicle on PND 56 *Transplacental initiation* Group 1: Saline/olive oil Group 2: Saline/Aroclor 1254 Group 3: NDMA/olive oil Group 4: NDMA/Aroclor 1254 Group 5: NNK/olive oil Group 6: NNK/Aroclor 1254 *Neonatal initiation* Group 7: NDMA/olive oil Group 8: NDMA/Aroclor 1254 Group 9: NNK/olive oil Group 10: NNK/Aroclor 1254 Animals/group, NR	*Transplacental initiation* Lung tumours (M): 2/27, 3/30, 0/29, 10/28*, 1/27, 8/29** Lung tumours (F): 1/29, 2/30, 3/30, 4/30, 4/30, 5/29 *Neonatal initiation* Lung tumours (M): 11/28, 22/30***, 8/30, 10/30 Lung tumours (F): 16/27, 19/27, 4/30, 11/29****	*$P < 0.001$ (group 4 vs group 3) **$P = 0.026$ (group 6 vs group 5) ***$P = 0.016$ (group 8 vs group 7) ****$P = 0.039$ (group 10 vs group 9)	Purity, NR The classification of lung tumours was not provided
Aroclor 1254	Rat, Sprague-Dawley (M) 18 wk Preston *et al.* (1981)	*Initiation*: NDEA at 66 µg/mL in drinking-water for 5 wk *Promotion*: Aroclor 1254 or Aroclor 1254 from which PCDFs were removed at 100 mg/kg diet, or control diet 40/group	Hepatocellular carcinoma: NDEA alone, 5/32 NDEA + Aroclor 1254, 21/33* NDEA + Aroclor 1254 with PCDFs removed, 27/32*	*$P < 0.05$, χ^2 analysis	
Aroclor 1254	Rat, Sprague-Dawley (M) 19 wk Vansell *et al.* (2004)	*Initiation*: DIPN (2.5 g/kg bw, s.c.) *Promotion*: 1 wk later, Aroclor 1254 at 100 mg/kg diet for 19 wk 24/group	*Thyroid* Cystic adenoma: 0/24, 2/22 Follicular adenoma: 5/24, 9/22 Follicular carcinoma: 1/24, 0/22 "Complete carcinoma": 0/24, 4/22*	*$P < 0.05$	Uncertainty in classification of one type of thyroid tumour as "complete carcinoma"

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Kanechlor 400	Rat, Donryu (F) 6 mo Kimura *et al.* (1976)	*Initiation*: MDAB (600 mg/kg diet) for 2 mo, rats aged 11–15 wk Treatment with Kanechlor 400 at 400 mg/kg diet before, during, or after MDAB Two groups were treated with Kanechlor 400 or MDAB only 25/group; 10 untreated controls	Hepatocellular carcinoma: MDAB alone, 2/15 MDAB followed by Kanechlor 400, 7/11* Kanechlor 400 followed by MDAB, 0/9 MDAB/Kanechlor 400 together, 0/11 Kanechlor 400 alone, 0/12 Untreated controls, 0/7	[*$P < 0.05$] vs MDAB-only group	The authors indicated that the incidence in the group receiving MDAB followed by Kanechlor 400 was significantly different from that in all other groups, using *t*-test, but the Working Group noted that this test cannot be used for binomial data
Kanechlor 500	Rat, Wistar (M) 40 or 52 wk Nishizumi (1979)	*Initiation*: NDEA at 50 mg/L in drinking-water for 2 wk *Promotion*: 1 wk later, 0.1 mL of 10% Kanechlor 500 in olive oil, by gavage, twice per week for 12 wk, then maintained until 40 or 52 wk after start of study 7–8/group per time-point	Hepatocellular tumours (mainly carcinomas): *40 wk:* NDEA + olive oil: 0/8 NDEA + Kanechlor 500: 6/7* (3.3 tumours/rat)** *52 wk:* NDEA + olive oil: 0/8 NDEA + Kanechlor 500: 8/8* (6.9 tumours/rat)**	*[$P < 0.05$] **$P < 0.01$	
Unspecified PCB mixture	Rat, F344 (M) 32 wk Hirose *et al.* (1981)	*Initiation*: 0.1% EHEN in drinking-water for 2 wk *Promotion*: 0 or 0.05% unspecified PCB mixture in diet for 32 wk UN 1 wk after starting PCBs 20–21/group	Hepatocellular carcinoma: EHEN only, 7/21 EHEN + PCB, 19/19 Renal cell tumours [benign]: EHEN, 18/21 EHEN + PCB, 12/19	$P < 0.001$ NS	PCB mixture: Kanegafuchi Chemical Co., Osaka, Japan No renal cell carcinomas were observed Statistical analysis, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Unspecified PCB mixture	Rat F344 (M) 32 wk Arai *et al.* (1983)	*Initiation*: NDMA (0.04% in diet) for 2 wk *Promotion*: 2 wk later, 500 mg/kg diet PCB mixture (or a basal diet) for 28 wk; UN 1 wk after starting PCBs 20/group	*Liver* Hyperplastic or neoplastic nodules (combined): NDMA, 5/18 NDMA + UN, 7/20 NDMA + PCBs, 10/11* NDMA + PCBs + UN, 7/7* Hepatocellular carcinoma: NDMA, 0/18 NDMA + UN, 0/20 NDMA + PCBs, 3/11* NDMA + PCBs + UN, 1/7 *Kidney* Nephroblastoma: NDMA, 17/18 NDMA + UN, 18/20 NDMA + PCBs**, 4/11 NDMA + PCBs + UN**, 3/7	*[$P < 0.05$] vs control group **[$P < 0.05$] vs control group (decrease)	PCB mixture: Kanegafuchi Chemical Co., Osaka, Japan Statistical analysis, NR Significant mortality in some groups, especially in the group receiving NDMA + PCBs + UN
PCBs with other modifying agents					
Aroclor 1254	Mouse, C57BL/10ScSn and DBA/2 2, 4, 8, and 12 mo Smith *et al.* (1990)	Injection with Fe (Fe-dextran, 12 mL/kg; Fe, 600 mg/kg bw, s.c.) or dextran followed 7 days later by Aroclor 1254 at 100 mg/kg diet for 2 mo (5 mice/group), 4 mo (C57 only, 5 mice/group), 8 mo (10 mice/group for C57; 5–7 group for DBA), or 12 mo (C57 only, 15–19/group)	*Hepatocellular adenoma:* 4 mo: Aroclor 1254, 0/5 Aroclor 1254 + Fe, 1/5 8 mo (C57): Aroclor 1254, 0/10 Aroclor 1254 + Fe, 7/9* 12 mon: Aroclor 1254, 0/16 Aroclor 1254 + Fe, 15/18* *Hepatocellular carcinoma:* 12 mo only: Aroclor 1254, 1/16 Aroclor 1254 + Fe, 7/18*	*[$P < 0.05$]	Statistical analysis, NR No effects of iron and Aroclor 1254 in DBA/2 mice

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Aroclor 1254	Mouse, C57BL/10ScSn 8 and 12 mo Smith *et al.* (1995)	Injection with Fe-dextran (Fe, 600 mg/kg bw, s.c.) or dextran, followed 3 days or 1 wk later by Aroclor 1254 at 100 mg/kg diet; for 8 mo (10/group) or 12 mo (15–19/group) Group 1: Aroclor Group : Aroclor + Fe	*8 mo:* Group 1: 0/10 (hepatocellular tumours); Group 2: 7/9* (hepatocellular adenoma) *12 mo:* Group 1: 0/16 (hepatocellular tumours); Group 2: 15/18* (hepatocellular adenoma) and 7/18* (hepatocellular carcinoma)	*[$P < 0.05$]	Statistical analysis, NR
Aroclor 1254	Mouse, C57BL/6J (M), *Cyp1a2*$^{-/-}$ or $^{+/+}$ (wildtype) 57 wk Greaves *et al.* (2005)	Injection with Fe-dextran (Fe, 800 mg/kg bw; route NR) followed by Aroclor 1254 at 100 mg/kg diet for 57 wk Fe + Aroclor 1254, 10/group Fe-only, 5/group	Liver adenoma: Fe-only: *Cypla2*$^{+/+}$: 0/5 *Cypla2*$^{-/-}$: 0/5 Fe + Aroclor: *Cypla2*$^{+/+}$: 5/10* *Cypla2*$^{-/-}$: 0/10	*[NS]	Statistical analysis, NR
Kanechlor 400	Mouse, A/J (M) 24 wk Nakanishi *et al.* (2001)	Single dose of Kanechlor 400 (2.5 mg/kg bw, i.p.) or DMSO vehicle injected into mice aged 6 wk. Mice were then injected with 1-nitropyrene at 1575 mg/kg bw (total dose of all injections) or DMSO vehicle (i.p., 3×/wk), 17 injections. Mice killed 18 wk after final injection of 1-nitropyrene 8–20/group	*Bronchioloalveolar lesions* Incidence (average number): DMSO control: 0/8 (0) Kanechlor 400: 2/10 (0.4) 1-Nitropyrene: 16/20 (1.8) Kanechlor 400 + 1-nitropyrene: 13/13 (3.2)* Number: DMSO control: 0 Kanechlor 400: 2 hyperplasias, 2 adenomas; 1-Nitropyrene: 10 hyperplasias, 20 adenomas, 3 adenocarcinomas; 1-Nitropyrene + Kanechlor 400: 15 hyperplasias, 23 adenomas, 8 adenocarcinomas	*$P < 0.01$ compared with 1-nitropyrene group	Statistical analysis, NR for incidence and number of lesions

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Kanechlor 400 and Kanechlor 500	Mouse, dd (M) 24 wk Nagasaki *et al.* (1975)	Dietary administration for 24 wk: α-BHC (250 mg/kg) α-BHC (250 mg/kg) + Kanechlor 500 (250 mg/kg) α-BHC (250 mg/kg) + Kanechlor 400 (250 mg/kg) α-BHC (100 mg/kg) α-BHC (100 mg/kg) + Kanechlor 500 (250 mg/kg) α-BHC (100 mg/kg) + Kanechlor 500 (100 mg/kg) α-BHC (100 mg/kg) + Kanechlor 400 (250 mg/kg) α-BHC (100 mg/kg) + Kanechlor 400 (100 mg/kg) α-BHC (50 mg/kg) α-BHC (50 mg/kg) + Kanechlor 500 (250 mg/kg) α-BHC (50 mg/kg) + Kanechlor 500 (100 mg/kg) α-BBC (50 mg/kg) + Kanechlor 400 (250 mg/kg) α-BHC (50 mg/kg) + Kanechlor 400 (100 mg/kg) Kanechlor 500 (250 mg/kg) Kanechlor 500 (100 mg/kg) Kanechlor 400 (250 mg/kg) Kanechlor 400 (100 mg/kg) 20–38/group	*Liver* Nodular hyperplasia: 30/38, 16/20, 26/30, 0/20, 8/25, 3/24, 4/29, 0/27, 0/20, 9/30, 0/28, 0/28, 0/27, 0/20, 0/20, 0/20, 0/20 Hepatocellular carcinoma: 10/38, 11/20*, 15/30*, 0/20, 1/25, 0/24, 0/29, 0/27, 0/20, 2/30, 0/28, 0/28, 0/27, 0/20, 0/20, 0/20, 0/20	*[$P < 0.05$] compared with α-BHC (250 mg/kg) group	The chemical is erroneously reported as benzene hexachloride and is actually hexachlorocyclohexane Statistical analysis, NR

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
Kanechlor 500	Mouse, dd (M) 24 wk Ito *et al.* (1973)	BHC, (α, β, or γ isomers) (50, 100 or 250 mg/kg diet) for 24 wk ± Kanechlor 500 (250 mg/kg diet) for 24 wk 25–30/group	*Liver nodular hyperplasia* α-BHC: 0/28, 0/26, 23/30 α-BHC + Kanechlor 500: 9/30, 8/25*, 21/26 β-BHC: 0/28, 0/26, 0/26 β-BHC + Kanechlor 500: 0/29, 5/30*, 16/29* *Hepatocellular carcinoma* α-BHC: 0/28, 0/26, 8/30 α-BHC + Kanechlor 500: 2/30, 1/25, 15/26* β-BHC: 0/28, 0/26/, 0/26 β-BHC + Kanechlor 500: 0/29, 1/30, 6/29* γ-BHC (all doses) and γ-BHC (all doses) + Kanechlor 500: no tumours (0/26–30)	*[$P < 0.05$]	The chemical is erroneously reported as benzene hexachloride and is actually hexachlorocyclohexane Statistical analysis, NR
PCB-77	Rat, Sprague-Dawley (F) 10.5 wk Nesaretnam *et al.* (1998)	Single dose of DMBA at 10 mg by gavage in 0.5 mL corn oil at age 50 days PCB-77 treatment: single dose at 10 mg/kg bw by gavage at the same time as DMBA, then in the diet at 500 mg/kg for one additional wk ($n = 2 \times 20$); or DMBA only ($n = 2 \times 20$) Rats were then fed either a low-fat (5%) ($n = 2 \times 20$) or a high-fat (20%) diet ($n = 2 \times 20$) Total: 4 groups of 20 rats Group 1: DMBA+PCB-77 + low fat Group 2: DMBA+PCB-77 + high fat Group 3: DMBA + low fat Group 4: DMBA + high fat	Mammary gland tumours (mainly mammary ductal carcinoma)	Number of palpable tumours: $P < 0.005$ for group 2 vs group 4 and group 1 vs group 3 at 8, 9, and 10 wk Incidence at 10.5 wk: $P < 0.05$ for group 1 (60%) vs group 3 (15%)	It was unclear whether the rats not treated with PCB-77 were given the vehicle instead Data were presented graphically

Table 3.13 (continued)

PCB congener or mixture	Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%), and/or multiplicity of tumours	Significance	Comments
PCB-126, PeCDF, and TCDD	Rat, Harlan Sprague-Dawley (F) 104 wk NTP (2006e)	PCB-126, TCDD and PeCDF in corn oil : acetone (99 : 1) by gavage 5 days/wk for 104 wk at doses of: 0 ng TEQ/kg bw (controls); 10 ng TEQ/kg bw (3.3 ng/kg TCDD, 6.6 ng/kg PeCDF, 33.3 ng/kg PCB 126); 22 ng TEQ/kg bw (7.3 ng/kg TCDD, 14.5 ng/kg PeCDF, 73.3 ng/kg PCB 126); 46 ng TEQ/kg bw (15.2 ng/kg TCDD, 30.4 ng/kg PeCDF, 153 ng/kg PCB-126); and 100 ng TEQ/k bw (33 ng/kg TCDD, 66 ng/kg PeCDF, 333 ng/kg PCB 126) 81 rats/group Interim evaluations: up to 10 rats/group were evaluated at 14, 31, and 53 wk	*Liver* Hepatocellular adenoma: 0/53, 1/53, 1/53, 1/53, 11/51* Cholangiocarcinoma: 0/53, 0/53, 2/53, 7/53*, 9/51** *Lung* Cystic keratinizing epithelioma: 0/53, 0/53, 0/53, 2/53, 20/53*	*$P < 0.001$ $P < 0.001$ (trend) *$P = 0.011$ **$P < 0.001$ $P < 0.001$ (trend) *$P < 0.001$ $P < 0.001$ (trend)	*Non-neoplastic lesions* Liver: hepatocyte hypertrophy, multinucleated hepatocytes, pigmentation, inflammation, diffuse fatty change, bile duct hyperplasia, oval cell hyperplasia, nodular hyperplasia, eosinophilic focus, cholangiofibrosis, bile duct cysts, necrosis, portal fibrosis, mixed cell focus, and toxic hepatopathy Lung: squamous metaplasia

DIPN, *N*-nitroso diisopropanolamine; DMBA, 7,12-dimethylbenz[*a*]anthracene; EHEN, *N*-ethyl-*N*-hydroxyethylnitrosamine; i.p., intraperitoneal; MDAB, 3′-methyl-4-dimethylaminoazobenzene; MNNG, *N*-methyl-*N*'-nitrosoguanidine; mo, month; MNU, *N*-methyl-*N*-nitrosourea; NDEA, *N*-nitrosodiethylamine; NDMA, *N*-nitrosodimethylamine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; NR, not reported; NS, not significant; PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; s.c., subcutaneous; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; TPA, 12-*O*-tetradecanoylphorbol-l3-acetate; UN, unilateral nephrectomy; wk, week

carcinoma, cholangioadenoma, cholangiocarcinoma, or hepatoblastoma. [The classification of tumours of the lung was not described.] In NDEA-treated DBA/2NCR mice and B6D2F1 mice, Aroclor 1254 did not affect the incidence or multiplicity of tumours of the liver (all or any of the various types) when compared with mice receiving NDEA only. In NDEA-treated C57BL/6 mice, Aroclor 1254 increased the incidences of tumours of the liver (all types combined) and of hepatocellular adenoma. The incidence or multiplicity of tumours of the lung was not affected by treatment with NDEA and Aroclor 1254 in any strain when compared with mice receiving NDEA only.

Poland *et al.* (1982) investigated whether Aroclor 1254 could promote *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)-initiated skin papillomas in female HRS/1 hairless mice. At age 8 weeks, mice were given 5 µmol of MNNG (in 50 µl of acetone) or the vehicle topically. Mice were then given a topical application of 1 mg of Aroclor 1254 (in 50 µl of acetone) per mouse, twice per week, for 20 weeks. There were 20 mice in the groups receiving MNNG plus Aroclor 1254, or Aroclor 1254 only, and 26 in the MNNG only-treated group. Aroclor 1254 did not promote MNNG-initiated tumours, and there was no neoplastic effect of Aroclor 1254 in non-initiated mice. [The statistical test was not reported.]

Beebe *et al.* (1993) investigated whether Aroclor 1254 could promote tumours of the lung and liver initiated by NDMA or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), either neonatally or transplacentally, in male and female Swiss (Cr:NIH) mice. For transplacental studies, pregnant mice were injected intraperitoneally with NNK at a dose of 0 (saline vehicle) or 100 mg/kg bw on days 15, 17, and 19 of gestation, or with NDMA at a dose of 0 (saline vehicle) or 10 mg/kg bw on day 19 of gestation. For the neonatal studies, infant mice were injected with NDMA (5 mg/kg bw), NNK (50 mg/kg bw), or saline vehicle on postnatal day 4. Mice were then given Aroclor 1254 by gavage (500 mg/kg bw) or olive oil vehicle for 44 weeks starting at age 56 days. There were 27–30 mice in all groups when the mice were killed at age 52 weeks. In females, transplacental exposure to NNK or NDMA plus Aroclor 1254 did not increase the incidence of tumours of the lung or liver compared with controls treated with NNK or NDMA only. In males, Aroclor 1254 increased the incidence of tumours of the lung (but not of the liver) initiated by either NDMA or NNK transplacentally. In females, Aroclor 1254 increased the incidence of tumours of the lung initiated neonatally by NNK, but not by NDMA. In males, Aroclor 1254 increased the incidence of tumours of the lung initiated neonatally by NDMA, but not by NNK. [The classification of tumours of the lung was not provided.]

(ii) Rat

Preston *et al.* (1981) investigated whether Aroclor 1254 promotes chemically-induced hepatocarcinogenesis in male Sprague-Dawley rats. Three groups of 40 rats were first given drinking-water containing NDEA at a concentration of 66 µg/mL for 5 weeks as an initiating agent. The rats were then fed an unrefined diet containing Aroclor 1254 at a concentration of 100 mg/kg, or Aroclor 1254 from which PCDFs (present as impurities) had been removed, or control diet. Rats were fed the diets for 18 weeks and then killed. Lesions of the liver were classified as foci of cellular alteration, neoplastic nodules, hepatocellular carcinoma, cholangioma, or cholangiocarcinoma. The administration of either Aroclor 1254, or Aroclor 1254 without PCDFs, significantly increased the incidences of NDEA-initiated hepatocellular carcinoma.

Vansell *et al.* (2004) studied whether Aroclor 1254 could promote tumours of the thyroid initiated by *N*-nitrosodiisopropanolamine (DIPN) in male Sprague-Dawley rats. Rats were first injected subcutaneously with DIPN at 0 (saline) or 2.5 g/kg bw. After a 1-week recovery period,

rats were fed a diet containing Aroclor 1254 at a concentration of 100 mg/kg for 19 weeks and then killed. Tumours were classified as thyroid cystic adenoma, thyroid follicular adenoma, thyroid follicular carcinoma, or "thyroid complete carcinoma." Aroclor 1254 only significantly increased the incidence of "thyroid complete carcinoma." [The Working Group noted the uncertainty of the classification of one type of thyroid tumour as "thyroid complete carcinoma."]

(c) Kanechlor 400 and Kanechlor 500

Rat

Kimura *et al.* (1976) gave female Donryu rats (age, 11–15 weeks) diets containing Kanechlor 400 or 3′-methyl-4-dimethylaminoazobenzene (MDAB) at a concentration of 400 or 600 mg/kg, respectively. Both agents were dissolved in olive oil before being added to the diet. There were five groups of 25 rats each. A first group was treated with Kanechlor 400 for 6 months, no treatment for 2 months, and then MDAB for 2 months; a second group was treated with MDAB for 2 months, no treatment for 2 months, then Kanechlor 400 for 6 months; a third group was treated with Kanechlor 400 for 6 months with MDAB given for the last 2 months, and no treatment for 4 months; a fourth group was treated with MDAB for 2 months and no treatment for 8 months; and a fifth group treated with Kanechlor 400 for 6 months and no treatment for 4 months. Additionally a sixth group of 10 rats was maintained for 10 months with no treatment. In all groups except that given MDAB only, body weight decreased markedly compared with untreated controls. Therefore, treatment with Kanechlor 400 was discontinued for 2 weeks after 3 months of treatment, and again for 4 weeks after the second 1 month of treatment. As for survival, 9, 11, 11, 15, 12 and 7 mice remained in groups 1 to 6, respectively. Only 2 out of 15 mice receiving MDAB only developed hepatocellular carcinoma compared with 7 out of 11 mice receiving MDAB followed by Kanechlor 400 [$P < 0.05$]. [The Working Group noted that the authors calculated the incidence in the group receiving MDAB then Kanechlor 400 compared to all other groups using a *t*-test, but it is not correct to use this test for binomial data.]

In a study to determine whether Kanechlor 500 could promote NDEA-initiated carcinogenesis, groups of 7–8 male Wistar rats were given drinking-water containing NDEA at a concentration of 50 mg/L for 2 weeks (Nishizumi, 1979). After a 1-week recovery period, the rats were given Kanechlor 500 (0.1 mL of 10% Kanechlor 500 in olive oil) by gavage twice per week for 12 weeks. Rats were then maintained without further treatment until being killed 40 and 52 weeks after the start of the experiment. Data were analysed using the Student *t*-test. The incidence [$P < 0.05$] and tumour multiplicity ($P < 0.01$) of hepatocellular tumours (mainly hepatocellular carcinomas) was significantly higher in rats given NDEA plus Kanechlor 500 than in rats given NDEA only, at both 40 and 52 weeks.

(d) Unspecified PCBs

Rat

In a study to examine the effect of an unspecified PCB mixture on hepatic and renal carcinogenesis induced by *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN), two groups of 20–21 male Fischer 344 rats were given drinking-water containing 0.1% EHEN for 2 weeks, or untreated drinking-water (Hirose *et al.*, 1981). After an unspecified time, rats were placed on a diet containing 0.05% PCBs [not further specified] for 32 weeks. One week after starting the experimental diet, the right kidney was removed (unilateral nephrectomy). All rats treated with EHEN plus PCBs (19 out of 19; $P < 0.001$) developed hepatocellular carcinoma, compared with one third (7 out of 21) of the rats treated with EHEN only. Treatment with PCBs had no effect on the incidence or number of EHEN-induced

tumours of the kidney (neoplastic nodules or renal cell tumours [all benign tumours]) compared with rats receiving EHEN only. No renal cell carcinoma was observed.

In a study to determine whether an unspecified PCB mixture could promote tumours of the liver and kidney induced by NDMA, four groups of 20 male Fischer 344 rats were fed a diet containing 0.04% NDMA for 2 weeks (Arai *et al.*, 1983). After a 2-week recovery period, rats were fed a diet containing PCBs [not further specified] at a concentration of 0 (basal diet) or 500 mg/kg for 28 weeks and then killed. In some groups, unilateral nephrectomy was performed at 5 weeks (1 week after starting the PCB containing diet). Tumours of the liver were classified as hyperplastic and neoplastic nodules, and hepatocellular carcinoma. Tumours of the kidney were classified as adenoma, adenocarcinoma, and nephroblastoma. In rats receiving NDMA plus PCBs, the incidences of liver hyperplastic or neoplastic nodules (combined) and of hepatocellular carcinoma (only in non-nephrectomized rats) were higher than in the respective controls. The administration of PCBs, either with or without nephrectomy, decreased the incidence of nephroblastoma. [The Working Group noted that no statistical analysis was reported and that there appeared to be significant mortality in some groups, especially in the group receiving NDMA plus PCBs plus unilateral nephrectomy.]

3.3.2 Studies with other modifying agents

(a) PCB-77

Rat

Nesaretnam *et al.* (1998) investigated whether dietary fat could influence the effect of PCB-77 on DMBA-induced tumours of the mammary gland in female Sprague-Dawley rats. Groups of 20 female rats were given DMBA (10 mg in 0.5 mL corn oil) by gavage at age 50 days. Two groups were also given a simultaneous dose of PCB-77 at 10 mg/kg bw by gavage, then a diet containing PCB-77 at a concentration of 500 µg/g corn oil for an additional week. Two groups were not exposed to PCB-77. [It was unclear whether these rats were given the vehicle instead of PCB-77.] The four groups (treated and not treated with PCB-77) were then fed either a low-fat (5%) or a high-fat (20%) purified diet. [Fat was substituted for dextrose on a weight basis rather than on a caloric basis.] Rats were palpated weekly for tumours of the mammary gland and were killed 10.5 weeks after administration of DMBA. Tumours at autopsy were mainly classified as mammary ductal carcinoma. The number of palpable tumours of the mammary gland was significantly higher in rats fed a high-fat diet plus PCB-77 than in rats fed a high-fat diet only, at 8, 9, and 10 weeks. Similarly, the incidence of tumours of the mammary gland was higher in rats fed a low-fat diet plus PCB-77 (~60%) than in rats fed a low-fat diet (~15%) only, at 10.5 weeks. [Data were presented graphically.]

(b) Aroclor 1254

Mouse

Smith *et al.* (1990) investigated whether iron (Fe) and/or Aroclor 1254 could influence liver carcinogenesis in male C57BL/10ScSn and DBA/2 mice. Mice (age 7–10 weeks) were first injected subcutaneously with Imferon, an Fe–dextran complex (12 mL/kg; dose of Fe, 600 mg/kg bw) or an equivalent volume of dextran C solution in water (200 mg/mL). After 7 days, mice were fed a diet mixed with 2% corn oil containing Aroclor 1254 at a concentration of 100 mg/kg for 2 (5 mice/group), 4 (C57 only, 5 mice/group), 8 (C57, 10 mice/group; DBA, 5–7 mice/group), or 12 months (C57 only, 15–19 mice/group) before being killed. Tumours were classified as hepatocellular adenoma or hepatocellular carcinoma. Higher incidences of hepatocellular tumour were observed in C57 mice receiving both Fe and Aroclor 1254 at 8 months (adenomas) and 12

months (adenomas and carcinomas) compared with those receiving Aroclor 1254 only. [No statistical analyses were reported.]

Smith *et al.* (1995) studied the influence of Fe and/or Aroclor 1254 on liver carcinogenesis in male C57BL/10ScSn mice [age of mice not reported]. Mice were subcutaneously injected a Fe–dextran solution (100 mg/mL Fe, and 100 mg/mL dextran; dose of Fe, 600 mg/kg bw) or the equivalent dextran solution only. After 3 days or 1 week, mice were fed a diet containing Aroclor 1254 (0.01% of diet) and corn oil (2%) for 8 months (10 mice/group) or 12 months (15–19 mice/group). Tumours were classified as nodules [hepatocellular adenoma] or hepatocellular carcinoma. Higher incidences of hepatocellular tumours were observed in mice receiving Aroclor 1254 plus Fe for 8 months (adenomas) and 12 months (adenomas and carcinomas) than in mice receiving Aroclor 1254 only. [No statistical analyses were reported.]

Greaves *et al.* (2005) studied the effects of deletion of the *Cyp1a2* gene on the induction of tumours of the liver by Aroclor 1254 and Fe in male C57BL/6J mice. *Cyp1a2* knockout $^{(-/-)}$ and wildtype $^{(+/+)}$ mice were given a Fe–dextran solution (Fe, 800 mg/kg bw) [route not reported], followed by a diet containing Aroclor 1254 at 100 mg/kg for 57 weeks or until death. There were 10 mice in the Aroclor 1254-treated groups and 5 mice in the control groups receiving Fe only. Liver tumours were classified as adenomas. No tumours were observed in *Cyp1a2* $^{(-/-)}$ mice or in *Cyp1a2* $^{(+/+)}$ wildtype mice not receiving Aroclor 1254. No tumours were seen in the 10 *Cyp1a2* $^{(-/-)}$ mice receiving Aroclor 1254, but 5 out of 10 [not significant] of the wildtype mice receiving Aroclor 1254 developed liver adenoma. [No statistical analyses were provided.]

(c) Kanechlor 400 and Kanechlor 500

Mouse

Nakanishi *et al.* (2001) examined the effects of Kanechlor 400 on lung tumorigenesis induced by 1-nitropyrene in male A/J mice. Mice (age, 6 weeks) were given a single intraperitoneal dose of Kanechlor 400 at 0 (corn oil vehicle) or 2.5 mg/kg bw. Mice were then given 1-nitropyrene or the DMSO vehicle, three times per week (17 intraperitoneal injections for a total dose of 1575 mg/kg bw). Mice were killed 18 weeks after the last injection of 1-nitropyrene. Numbers of mice per group were as follows: DMSO controls, 8; Kanechlor 400, 10; 1-nitropyrene, 20; 1-nitropyrene plus Kanechlor 400, 13. Lung lesions were classified as bronchioloalveolar hyperplasia, adenoma, or adenocarcinoma. The incidence of lesions of the lung was increased in both groups of mice receiving 1-nitropyrene. The average number of lesions, but not incidence, was significantly greater in the group receiving Kanechlor 400 plus 1-nitropyrene than in the group receiving 1-nitropyrene only.

Nagasaki *et al.* (1975) investigated whether co-administration of Kanechlor 400 or Kanechlor 500 and α-benzene hexachloride (α-BHC) [hexachlorocyclohexane] would affect the incidence of nodular hyperplasia of the liver and hepatocellular carcinoma in male dd mice. Mice were given diets containing α-BHC at a concentration of 50, 100, or 250 mg/kg, and/or Kanechlor 400 or Kanechlor 500 (100 or 250 mg/kg), for 24 weeks. Nodular hyperplasia and hepatocellular carcinoma were observed. The incidence of hepatocellular carcinoma was higher [$P < 0.05$] in mice receiving 250 mg/kg α-BHC and the higher dose of Kanechlor 400 or Kanechlor 500, than in mice receiving only α-BHC at 250 mg/kg. No tumours were induced by Kanechlor 400 or Kanechlor 500 only. [Statistical analyses were not reported.]

A study by Ito *et al.* (1973) examined the effects of co-administration of Kanechlor 500 and one isomer of benzene hexachloride (BHC)

[hexachlorocyclohexane] on the incidence of nodular hyperplasia of the liver and hepatocellular carcinoma. Groups of male dd mice (age, 8 weeks) were given diets containing α-, β-, or γ-BHC (50, 100 or 250 mg/kg) for 24 weeks, with or without Kanechlor 500 (250 mg/kg). In some groups, Kanechlor 500 promoted the incidence of nodular hyperplasia and hepatocellular carcinoma induced by α-BHC and β-BHC. [Statistical analyses were not reported.]

(d) PCB-126, PeCDF, and TCDD

Rat

In a study by the NTP, groups of 81 female Harlan Sprague-Dawley rats were given a mixture of TCDD, PeCDF, and PCB-126 by gavage, 5 days per week, for up to 2 years (NTP, 2006e). Up to 10 rats per group were evaluated after 14, 31, and 53 weeks. Doses were formulated by using the WHO TEF values of 1.0 for TCDD, 0.1 for PCB-126, and 0.5 for PeCDF. Specific target doses were: "10 ng TEQ/kg bw" (TCDD, 3.3 ng/kg; PeCDF, 6.6 ng/kg; PCB-126, 33.3 ng/kg), "22 ng TEQ/kg bw" (TCDD, 7.3 ng/kg; PeCDF, 14.5 ng/kg; PCB-126, 73.3 ng/kg), "46 ng TEQ/kg bw" (TCDD, 15.2 ng/kg; PeCDF, 30.4 ng/kg; PCB-126, 153 ng/kg), and "100 ng TEQ/kg bw" (TCDD, 33 ng/kg; PeCDF, 66 ng/kg; PCB-126, 333 ng/kg). Rats in the control group received the corn oil : acetone vehicle (99 : 1; 2.5 mL/kg bw) only. After 2 years, there were statistically significant increases ($P < 0.001$) in the incidences of cholangiocarcinoma, hepatocellular adenoma, and cystic keratinizing epithelioma of the lung in the group at 100 ng TEQ/kg bw. The incidence of cholangiocarcinoma was also significantly increased ($P = 0.011$) in the group at 46 ng TEQ/kg. In addition, there was a significant trend in the incidence of these three types of neoplasm with increasing dose.

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4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Absorption, distribution, metabolism, and excretion

In this Section, the most recent Ballschmiter & Zell (BZ) nomenclature was used throughout (see Mills *et al.*, 2007). For the full corresponding IUPAC nomenclature, the reader is referred to Section 1.1, Tables 1.1–1.3. For the methyl sulfonyl metabolites, and wherever the nomenclature reported is unclear, the name of the metabolite is given as reported in the article, followed by, where appropriate, the abbreviation as well as the structural name (Maervoet *et al.*, 2004; Grimm *et al.*, 2015).

4.1.1 Absorption

(a) Oral exposure

(i) Humans

The absorption of polychlorinated biphenyls (PCBs) was studied in four breastfed infants in Sweden by Dahl *et al.* (1995). Absorption was measured by comparing the estimated total intake and the excretion in faeces for 48 hours, at 1, 2, and 3 months postpartum. The concentrations of 56 congeners in maternal milk were determined. For tetrachlorosubstituted to octachlorosubstituted congeners, absorption was found to be close to 100%, while absorption of trichlorinated congeners was 60–98%, probably due to the low levels at which they were present and ensuing analytical difficulties in detection. [Another possible explanation could be metabolism of the trichlorinated congener.]

The gastrointestinal absorption of 10 congeners from food was investigated using a mass balance approach in seven individuals aged 24–81 years with different contaminant body burdens (Schlummer *et al.*, 1998). The difference between ingested and excreted amounts of the chlorinated compounds was defined as net absorption. Nearly complete net absorption was observed for PCB-28, PCB-52, PCB-77, PCB-101, and PCB-126. Absorption of PCB-105, PCB-138, PCB-153, and PCB-180 was > 60% in most volunteers, but limited absorption was observed in the three older subjects. In all cases, absorption of PCB-202 was < 52%.

(ii) Experimental systems

Several reports have been published on the dietary absorption of PCBs, mostly individual congeners. Gastrointestinal absorption of congeners with between one and six chlorine atoms has been investigated by monitoring faecal excretion in rats fed individual congeners at doses ranging from 5 to 100 mg/kg bw. Absorption of the administered dose was > 90% for all 20 congeners tested (Albro & Fishbein, 1972). Metabolic studies in rodents given oral doses of various radiolabelled PCBs with three to six chlorine atoms (i.e. PCB-31, PCB-47, PCB-85, PCB-101, and PCB-153) indicated that gastrointestinal

absorption was highest for the trichlorobiphenyl congener (about 94% of the administered dose), and lowest for the hexachlorobiphenyl PCB-153 (28%) (Bergman *et al.*, 1982). In a study by Tanabe *et al.* (1981), absorption efficiency was 95% for dichlorobiphenyls, but only 75% for octachlorobiphenyls. These data suggested that, in rats, absorption of PCBs decreases as the number of chlorine atoms increases.

(b) Inhalation

(i) Humans

There is indirect evidence for absorption of PCBs via inhalation in humans; several congeners have been detected in body fluids of people exposed in occupational settings or frequenting contaminated buildings, such as schools, where air concentrations of PCBs have also been measured (Wolff, 1985; Wolff *et al.*, 1992; Schwenk *et al.*, 2002; Liebl *et al.*, 2004).

(ii) Experimental systems

Hu *et al.* (2010) used a nose-only exposure system to assess the time course of PCB vapour uptake from commercial products in animals. Rats (average weight, 188 g) were exposed to vapours of Aroclor 1242 (PCB concentration, 2.4 mg/m^3; total amount, 40 µg) for a total of 2 hours, with a 1-hour break, and killed at 0, 1, 3, 6, and 12 hours after exposure. Congeners detected in tissues included mostly PCBs with mono- or di-*ortho*-substitution, ranging from mono- to pentachlorobiphenyls, with the majority being tri- and tetrachlorobiphenyls. PCB-20 + PCB-28 co-elution was most abundant in every tissue. When compared with the air mixture, most of the material retained in the tissues had shifted from mono- and dichlorinated PCBs to tri- and tetra- or even more highly chlorinated biphenyls. The amount of PCBs measured in the five tissues collected (liver, lung, blood, adipose tissue, and brain) was 5 µg per rat. The measured body burden (i.e. the sum of PCBs loaded at the end of exposure) was 33 µg per rat, suggesting pulmonary absorption of close to 100%. Casey *et al.* (1999) found that uptake of PCBs was greater by inhalation than by ingestion in a comparison of rats exposed to Aroclor 1254 for 30 days via inhalation (0.9 µg/m^3) or in the diet (0.436 µg/g).

(c) Dermal exposure

(i) Humans

Studies on exposure of capacitor workers to PCBs suggested that these compounds are well absorbed by skin contact (Wolff, 1985). Skin samples collected from human cadavers and exposed in vitro to [^{14}C]-labelled Aroclor 1254 and Aroclor 1242 retained 43–44% of the administered dose over a 24-hour period when the mixtures were formulated in water (Wester *et al.*, 1990, 1993). A lower retention was observed when PCBs were formulated in mineral oil or adsorbed on contaminated soil.

(ii) Experimental systems

In rhesus monkeys, percutaneous absorption in vivo of [^{14}C]-labelled Aroclor 1242 and Aroclor 1254 formulated in mineral oil was 20.4 ± 8.5% and 20.8 ± 8.3% of the administered dose, respectively, as determined by urinary and faecal excretion of radiolabel for 30 days after topical application (Wester *et al.*, 1990).

In rats given selected mono-, di-, tetra- and hexachlorobiphenyls as a single dermal dose (0.4 mg/kg bw), dermal penetration varied inversely with the degree of chlorination Garner & Matthews (1998). At 48 hours, dermal penetration ranged from about 100% for the monochlorobiphenyl to about 30% for the hexachlorobiphenyl.

In rats given a topical dose of [^{14}C]-labelled PCB-77 or PCB-153, absorption at 24 hours after dosing ranged from 5% to 8% for both compounds (Hughes *et al.*, 1992). Skin retention was 3–31% for PCB-77 and 3–12% for PCB-153. Dermal absorption was similar for all application forms (solid, aqueous paste, aqueous suspension, dissolved in ethanol). For PCB-153, absorption

was significantly higher when PCB-153 was applied as a solid compared with in ethanol.

Male F344 rats were given single doses (0.4 mg/kg bw) of [^{14}C]-labelled mono-, di-, tetra- and hexachlorobiphenyls applied to 1 cm^2 areas of the dorsal skin (Garner *et al.*, 2006). The more highly chlorinated PCBs were slowly absorbed and accumulated in the adipose tissue and skin. Excretion of absorbed radiolabel varied with chlorine content, ranging from 27% to about 100% at 2 weeks after dosing (Garner *et al.*, 2006).

4.1.2 Distribution

The distribution of PCBs is dependent on the structure and the physicochemical characteristics of the individual congeners, and also on dose.

(a) Humans

No studies of quantitative distribution in humans after controlled exposure to PCBs were available to the Working Group. However, some information existed regarding the concentration of PCBs in human tissues and biological fluids after occupational or dietary exposure. PCBs distribute preferentially to adipose tissue and concentrate in human breast milk due to its high fat content. The pattern of congeners observed in tissues does not correspond with the profiles of commercial PCB mixtures.

The most commonly detected PCBs in plasma and in adipose tissue of occupationally exposed individuals are the hexa- and heptachlorobiphenyls. PCB congeners with chlorine atoms in the 4 and 4′ positions were generally found at relatively high concentrations, while PCBs with nonsubstituted 3,4-positions on at least one ring were present at lower concentrations (ATSDR, 2000).

In Greenlanders exposed through high consumption of fat from sea mammals, the most abundant PCB congeners found in adipose tissue, plasma, and liver were PCB-138, PCB-153, and PCB-180 (Dewailly *et al.*, 1999).

Some studies focused on transplacental transfer of PCBs, as determined by measurement of PCB concentrations and congener profiles in maternal blood, placenta and cord blood. Tsukimori *et al.* (2013) investigated concentrations of four non-*ortho* PCBs (PCB-77, PCB-81, PCB-126, PCB-169) in maternal blood, placenta, and cord blood in 19 pregnant women from Fukuoka City, Japan. Mean concentrations were 3.95, 0.87, and 1.08 pg toxic equivalency (TEQ)/g lipid in maternal blood, placenta, and cord blood, respectively. Among specific congeners, PCB-126 showed the highest ratio for cord blood to maternal blood (0.3). PCBs are able to cross the placental barrier in humans, with PCB concentration in cord blood being 25–50% of that in maternal blood.

A study of 360 second-grade schoolchildren (a subgroup of the cohort in Hesse, Germany) in 1995 (Karmaus *et al.*, 2001a, b) found a significant dose-dependent relationship between the duration of breastfeeding (0, 1–4 weeks, 5–8 weeks, 9–12 weeks, > 12 weeks) and blood concentrations of all organochlorine compounds, including PCBs. Breastfeeding for more than 12 weeks was associated with a doubling of concentrations of organochlorine compounds in the children's blood.

Scheele *et al.* (1992) measured the concentrations of PCB-138, PCB-153, and PCB-180 in 38 children with leukaemia and 15 children in a control group. The PCB concentrations in bone marrow were higher by two- to threefold than those in fat tissue; however, there was no significant difference between PCB concentrations in bone marrow of children with leukaemia and of children in the control group.

PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, and PCB-180 were analysed in six post-mortem samples of human lung (Rallis *et al.*, 2012). The limit of quantification (LOQ) varied from 1.7–4.5 ng/g tissue. PCB-153 (detected in two cases), PCB-138 and PCB-180 (detected in three cases) were found at highest concentrations, ranging from < LOQ to 6.3 ng/g.

In 107 post-mortem samples of human brain (Mitchell *et al.*, 2012), eight congeners (PCB-28, PCB-95, PCB-105, PCB-118, PCB-138, PCB-153, PCB-170, and PCB-180) were analysed. PCB-138, PCB-153, and PCB-180 were most frequently detected, at average concentrations of 5.5–8 ng/g lipid. PCB-95 was mainly detected in samples from individuals with neurodevelopmental disorders with a known genetic basis, compared with neurologically typical controls.

In addition to the parent PCBs, hydroxylated metabolites have been detected in human serum and adipose tissue (Fernandez *et al.*, 2008). The concentrations of hydroxylated PCBs (OH-PCBs; 14 congeners), methylsulfonyl PCBs ($MeSO_2$-PCBs; 24 congeners), and parent PCBs (17 congeners) in five paired samples of human liver and adipose tissue were reported by Guvenius *et al.* (2002). The sum of OH-PCB congeners was higher in liver (7–175 ng/g lipid) than in adipose tissue (0.3–9 ng/g lipid), with 3′-OH-PCB-138 and 4′-OH-PCB-130 as the predominant OH-PCB metabolites. The sum of $MeSO_2$-PCBs was of the same order of magnitude as OH-PCB congeners in the same samples: 12–358 ng/g lipid and 2–9 ng/g lipid in liver and adipose tissue, respectively. The concentrations of parent PCBs were similar in liver and adipose tissue, at 459–2085 ng/g lipid and 561–2343 ng/g lipid, respectively.

Concentrations and congener profiles of PCBs and OH-PCBs in placenta samples from a population in Madrid, Spain, were reported by Gómara *et al.* (2012). The sum of PCB concentrations in placenta samples ranged from 943–4331 pg/g fresh weight, and their hydroxylated metabolites showed a 20-times lower concentration (53–261 pg/g fresh weight). PCB-52 and PCB-101 accounted for more than 44% of the total amount of PCBs. The OH-PCB profiles were dominated by 4-OH-PCB-187 and 4-OH-PCB-146, representing > 50% of the sum concentration of OH-PCBs in the placenta samples.

The concentration of OH-PCBs may comprise 10–20% of total PCBs in human serum, and as many as 38 different OH-PCBs were structurally identified in human plasma, pooled from 10 randomly selected male donors. Only a few of these make up the major proportion of the OH-PCBs present in human blood (Hovander *et al.*, 2002).

$MeSO_2$ metabolites of PCBs were investigated in serum samples from pregnant women from Slovakia and in a selected number of paired samples of cord blood (Linderholm *et al.*, 2007). The major methylsulfone in most samples was a non-identified $MeSO_2$-hexachlorinated biphenyl, followed by 4′-$MeSO_2$-PCB-101, 4′-$MeSO_2$-PCB-87, and 4-$MeSO_2$-PCB-149. The concentrations of $MeSO_2$-PCBs in maternal serum were about 1.5 times higher than in the corresponding cord serum on a lipid-weight basis. In samples of human adipose tissue, 4-$MeSO_2$-PCB-49 [4-$MeSO_2$-2,2′,4′,5-tetraCB; 4′-$MeSO_2$-PCB-49], 4-$MeSO_2$-PCB-101 [4′-$MeSO_2$-PCB-101; 4-$MeSO_2$-2,2′,4′,5,5′-pentaCB], and 3-$MeSO_2$-PCB-110 [5-$MeSO_2$-PCB-110; 3-$MeSO_2$-2,3′,4′,5,6- pentaCB] were the predominant $MeSO_2$ metabolites (Karásek *et al.*, 2007).

(b) Experimental systems

(i) PCB mixtures

Adult rhesus monkeys were given Aroclor 1248 as a single dose at 1.5 or 3.0 g per kg bw by gastric intubation, and killed after 4 days (Allen *et al.*, 1974). At the lowest dose tested, average concentrations found in liver, kidney, and brain were 25, 12, and 17 µg/g tissue, respectively. In another study, two groups of eight adult rhesus monkeys were exposed to diets containing Aroclor 1248 at 2.5 ppm (Allen & Barsotti, 1976). After 6 months of exposure, the monkeys were successfully bred. After 2 months, milk samples after birth were obtained from four lactating mothers exposed at 2.5 ppm. Concentrations of PCBs ranged from 0.154 to 0.397 µg per g milk in

three samples of milk fat, and reached 16.44 µg per g in milk fat in the fourth sample.

PCBs were analysed in blood, adipose tissue, liver, kidney and brain from female rhesus monkeys fed Aroclor 1254 at a daily dose of 0, 5, 20, 40, or 80 µg/kg bw for approximately 6 years (16 animals per group) (Mes *et al.*, 1995a). Offspring were nursed for 22 weeks and fed no additional PCBs until necropsy at approximately 120 weeks after birth. PCB concentrations in all tissues of the adult monkeys (mothers and offspring) increased with increasing dose. Mes *et al.* (1994) reported that for groups exposed to higher doses (≥ 40 µg/kg bw), tissues of infants from dosed dams contained higher concentrations of PCBs than tissues of infants from control dams. The PCB distribution pattern in tissues from a dosed mother/infant pair differed considerably. A larger percentage of heptachlorobiphenyls was found in the infants than in their dams.

In rats given a single dose of Aroclor 1254 at 500 mg/kg bw by gavage, the highest PCB concentrations were found in adipose tissue (996 µg/g wet weight), liver (116 µg/g wet weight), and brain (40 µg/g wet weight), indicating that PCBs are able to cross the blood–brain barrier (Grant *et al.*, 1971). The relative amounts of PCBs in the brain, liver, spleen, blood, testes, heart, kidney, and adipose tissue of rats killed 3 weeks after treatment were 10%, 16%, 20%, 21%, 22%, 24%, 36%, and 67%, respectively, of those found in animals killed after 2 days. In a subsequent long-term study, Grant *et al.* (1974) fed rats with Aroclor 1254 at a dietary concentration of 0, 2, 20, or 100 mg/kg feed and found highest concentrations of PCBs after 246 days in adipose tissue, with concentrations reaching 26.1 ± 2.9 µg/g wet tissue at the lowest contamination tested (2 mg/kg feed). Levels of PCBs in all tissues analysed were dose-related, and generally, the tissue concentrations did not increase significantly after 64 days of exposure. The residues present in the adipose tissue, liver, and brain had decreased by 64%, 75%, and 10% respectively, 182 days after removal of Aroclor 1254 at 2 mg/kg from the diet. Part of the decrease observed in the adipose tissue and the liver resulted from a dilution effect due to weight increase in these tissues.

The analysis of individual congeners in tissues of rats fed diets containing Aroclor 1254 for 84 days demonstrated a limited accumulation of PCB congeners with a low level of chlorine substitution (tri- and tetrachlorobiphenyls) (Nims *et al.*, 1994). In these rats, time- and dose-dependent increases in the relative concentrations of PCB-138 and PCB-153 were detected in the liver and adipose tissue. Increases in PCB-99 concentrations in hepatic and adipose tissues, and in PCB-156 in adipose tissue, were also observed.

Aroclor 1254 was given to pregnant rats once daily on days 7–15 of gestation (Curley *et al.*, 1973). The concentrations of PCBs found in fetuses were higher by twofold in the group at 50 mg/kg bw compared with the group at 10 mg/kg bw. The mean concentrations of PCB-derived components found in brain, liver, and kidney in weanlings aged 21 days (27 days after the last dose was given to the mother in the group at 10 mg/kg bw) were approximately 2, 4, and 2 µg/g wet tissue, respectively. Concentrations in milk sampled from the same group were between 16 and 25 µg/g.

Samples of brain, adipose tissue, and liver from rat pups and dams exposed to Aroclor 1254 were analysed by Shain *et al.* (1986). In adipose tissue, most congeners were detected at concentrations close to the feed concentration, but the following congeners accumulated to tissue concentrations 10-fold those in the feed: PCB-176, PCB-146, PCB-138 + PCB-168 + PCB 178 (co-eluted), and PCB-177. In the liver and the brain, the congeners present at the highest concentrations were PCB-85 and PCB-179 + PCB-188 (co-eluted). Bioaccumulation of congeners in the milk closely resembled that observed in fat samples from the dams. The chromatographic pattern

of bioaccumulated congeners in pup liver was different from that observed in the dams. The congener found at the highest concentration in samples of newborn rat brain was PCB-85. Shain *et al.* (1986) estimated that the transfer of PCBs through the mammary gland and milk in rats may be 100 times higher than the transfer across the placenta, resulting in a higher accumulation during lactation than during pregnancy.

Kodavanti *et al.* (1998) investigated the congener-specific distribution of PCBs in blood, brain, liver, and adipose tissue of adult rats given repeated doses of Aroclor 1254 (30 mg/kg bw per day; once per day, 5 days per week for 4 weeks). Total PCB congeners in control rat brain were < 0.02 µg/g tissue. Mean concentrations of total PCBs in treated rats in the frontal cortex, cerebellum, and striatum were 15.1, 13.1, and 8.2 µg/g tissue, respectively; those in the blood, liver, and adipose tissue were 1.6, 38.3, and 552 µg/g tissue, respectively. In addition to differential total uptake between tissues, there was differential accumulation of PCBs with respect to number of chlorine substituents. In all tissues, heavily (hexa- to nona-) chlorinated congeners were present in higher proportions than in the parent mixture, Aroclor 1254, while less highly (tetra- and penta-) chlorinated congeners were present to a lesser degree than their respective proportions in Aroclor 1254. This shift towards accumulation of heavily chlorinated congeners appeared to be more pronounced in the brain than in liver and fat.

In rats exposed via inhalation to vapour-phase PCBs generated from Aroclor 1242 for 10 days, much higher amounts of PCBs (× 400) were found in liver and lung than in blood (Hu *et al.*, 2010). PCB-20 + PCB-28 (co-eluted), PCB-49 + PCB-69 (co-eluted), PCB-52, PCB-60, PCB-61 + PCB-70 + PCB-74 + PCB-76 (co-eluted), PCB-66, PCB-83 + PCB-99 + PCB-112 (co-eluted), PCB-85 + PCB-116 + PCB-117 (co-eluted), PCB-90 + PCB-101 + PCB-113 (co-eluted), PCB-105, and PCB-118 were the major congeners in these tissues.

The presence of $MeSO_2$-PCB atropisomers was determined in liver, lung, and adipose tissues of rats orally exposed to Clophen A50. In all tissues analysed, especially lung, *para*-$MeSO_2$ PCBs were more abundant than *meta*-derivatives. An excess of the atropism 2(A_2) of 4-$MeSO_2$-PCB-149 – (*R*)-3-$MeSO_2$-PCB-149 – in lung extracts was observed (Larsson *et al.*, 2002). The enantiomeric enrichment of PCB atropoisomers was reported in selected tissues from rats exposed to Aroclor 1254 (Kania-Korwel *et al.*, 2006). Both PCB-95 and PCB-149 were enantiomerically enriched to a significant extent in adipose tissue, liver, and skin.

A few studies on complex mixtures such as Aroclor 1254 mention substantial retention of certain congeners in lung of treated mice (Anderson *et al.*, 1993).

In mice exposed to contaminated soil (retrieved from a Superfund site before remediation) through their bedding for 4 weeks, total PCB residues in skin and fat declined about 80% during the 4-week recovery period. PCB residues were detected in the ear skin (total PCBs, 208 mg/kg of tissue), trunk skin (total PCBs, 129 mg/kg of tissue), and in body fat (total PCBs, 370 mg/kg), confirming these tissues as important PCB reservoirs (Imsilp & Hansen, 2005).

(ii) Individual congeners

Several experiments carried out in mammals, including non-human primates, confirm the data obtained with complex mixtures. The congeners investigated were unlabelled or labelled PCB-3, PCB-5, PCB-15, PCB-30, PCB-31, PCB-47, PCB-65, PCB-77, PCB-101, PCB-116, PCB-118, PCB-126, PCB-153, and PCB-196 (Goto *et al.*, 1974a, b; Matthews & Anderson, 1975a, b; Abdel-Hamid *et al.*, 1981; Beran *et al.*, 1983; Shimada & Sawabe, 1984; Koga *et al.*, 1990; van Birgelen *et al.*, 1996; Pereg *et al.*, 2001; NTP, 2006a, b, 2010). In some cases, mixtures of individual congeners were used (Öberg *et al.*, 2002; NTP, 2006c, d). Taken together, the data indicated that an oral

dose of PCBs results in an initially high concentration in liver and serum, followed by a decrease in concentrations in the liver, and a concomitant increase in adipose tissue and lipid-rich tissues. This redistribution generally occurred during the first week after dosing, and the differences between the congeners were mainly dependent on the number of chlorine atoms (ATSDR, 2000). In rodents, the hepatic retention/accumulation of non-*ortho*-substituted PCBs such as PCB-126 may occur to a higher extent than in adipose tissue, including after long-term exposure (NTP, 2006a). This was not the case for congeners with chlorine atoms in *ortho* positions, such as PCB-153 (van Birgelen *et al.*, 1996; NTP, 2006a, b).

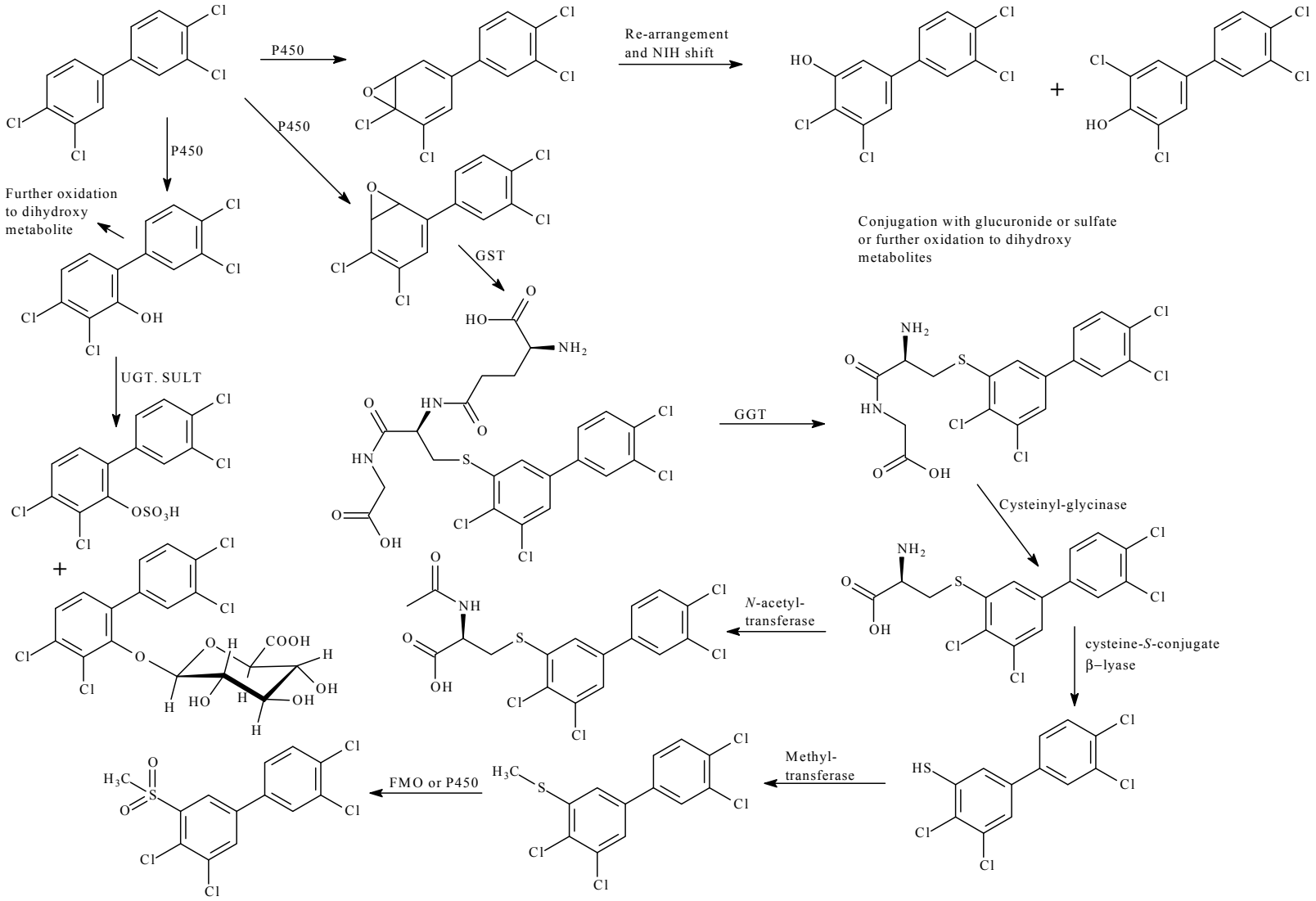
4.1.3 Metabolism

There is evidence that most known PCBs are subject to biotransformation (metabolism) in humans and other animals through enzymatic processes (Safe, 1993). Biotransformation is important for the eventual elimination of PCBs from the body, as most (but not all) of the metabolites are more water-soluble than the parent compound. As well as serving as substrates for biotransformation enzymes, some PCBs and PCB metabolites can interact with several drug-metabolizing enzymes as inducers or inhibitors, as discussed further below.

The first step in metabolism targets the biphenyl ring carbons, and is catalysed by cytochrome P450 (CYP) monooxygenase enzymes. Subsequent metabolism involves one or more of several other possible enzymatic pathways (James, 2001). Some of the major pathways of PCB metabolism are illustrated in Fig. 4.1, with PCB-77 as an example. Fig 4.2 shows structures of representative PCB metabolites. The rate and extent of biotransformation of a particular PCB congener depend upon its chlorination pattern, the number of chlorine substituents, the species, age, and sometimes sex of the animal, and in some cases whether or not the exposure is continuous or a single exposure. The number of chlorine substituents and substitution pattern determine how well a particular PCB congener binds to and can be metabolized by the biotransformation enzyme (Matthews & Dedrick, 1984). In general, congeners with more than four chlorine substituents are more slowly metabolized than those with four or fewer chlorines, and congeners with unsubstituted 3,4-positions in one or both rings are more readily metabolized than those without such substitution patterns (Hansen, 2001). Biotransformation enzymes with similar functions often differ between animal species in properties of substrate recognition and binding, which contributes to species differences in metabolism. Very young animals often have lower levels of several biotransformation enzymes than adults, resulting in age-related differences in metabolism (Hines, 2008). In rodents, sex affects the expression of several important biotransformation enzymes, particularly CYP, which can lead to sex-specific differences in PCB metabolism. The reason that continuous exposure to certain PCB congeners can affect rate and extent of metabolism is that such exposure can result in upregulation of expression of enzymes that biotransform PCBs, through receptor-mediated processes. PCBs that bind the aryl hydrocarbon receptor (AhR) (see Section 4.3.1) are known to induce CYP isoforms in the 1 family (CYP1A1, CYP1A2 and CYP1B1) as well as epoxide hydrolase, some isoforms of uridine diphosphate-glucuronosyltransferase (UGT) and glutathione *S*-transferase (GST) (Parkinson *et al.*, 1980; 1983). PCBs that bind the nuclears receptors, the pregnane-X receptor (PXR) and the constitutive androstane receptor (CAR) have been shown to induce CYP3A4 and CYP2B isoforms (Petersen *et al.*, 2007; Al-Salman & Plant, 2012).

In the context of carcinogenesis, biotransformation to electrophilic metabolites that are more chemically reactive than the parent PCB is likely to be an important component. Being more biotransformed, the metabolized congeners are more likely to undergo bioactivation.

Fig. 4.1 Metabolic pathways for polychlorinated biphenyls, showing PCB-77 (3,3′,4,4′-tetrachlorobiphenyl) as an example

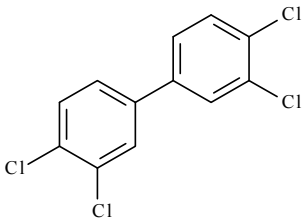


P450, cytochrome P450; UGT, UDP-glucuronosyltransferase; SULT, 3′-phosphoadenosine-5′-phosphosulfate-sulfotransferase; GST, glutathione-*S*-transferase; GGT, gamma-glutamyl transpeptidase; FMO, flavin monooxygenase

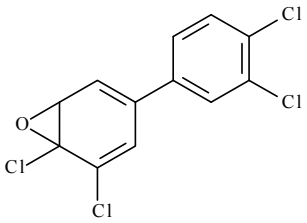
The NIH shift causes non-enzymatic migration of chlorine atoms to an adjacent carbon.

Compiled by the Working Group

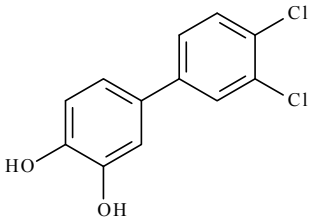
Fig. 4.2 Representative metabolites derived from PCB-77 (3,3′,4,4′-tetrachlorobiphenyl)



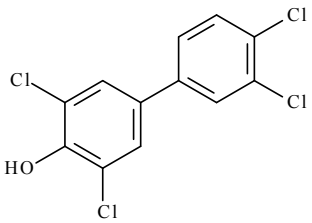
3,3',4,4'-tetrachlorobiphenyl (parent)



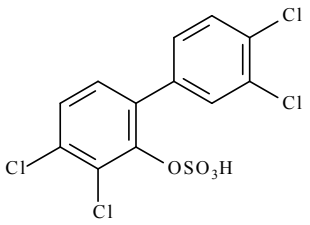
4,5-arene oxide of 3,3',4,4'-tetrachlorobiphenyl



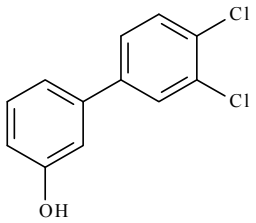
3',4'-dihydroxy-3,4-dichlorobiphenyl
(catechol metabolite)



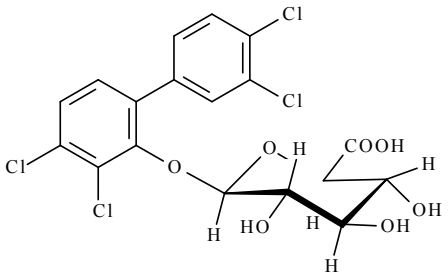
4'-hydroxy-,3,3',4,5'-tetrachlorobiphenyl



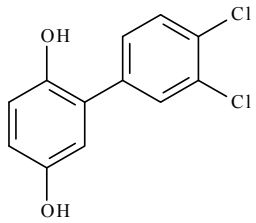
2'-hydroxy-3,3',4,4'-tetrachlorobiphenyl-2'-sulfate



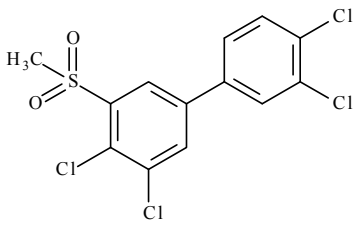
3'-hydroxy-3,4-dichlorobiphenyl



2'-hydroxy-3,3',4,4'-tetrachlorobiphenyl-2'-glucuronide



2',5'-dihydroxy-3,4-dichlorobiphenyl
(semiquinone metabolite)



5-methyl-sulfonyl-3,3',4,4'-tetrachlorobiphenyl
(methyl sulfone metabolite)

The following sections describe the different enzymatic pathways known to be involved in PCB metabolism.

(a) CYP

The first step in biotransformation of PCBs is introduction of oxygen, catalysed by one or more members of the CYP superfamily of monooxygenase enzymes (Guengerich, 2008). Two mechanisms are known, H• radical abstraction and recombination of the short-lived chlorobiphenyl radical with an OH• radical from the active site of CYP to give a hydroxylated (phenolic) metabolite, and formation of an arene oxide by addition of oxygen across an aromatic bond in the biphenyl ring. The arene oxide is an electrophilic metabolite that can rearrange non-enzymatically to form a phenolic metabolite. If one of the carbons that forms part of the arene oxide is substituted with chlorine then, during the non-enzymatic rearrangement, that chlorine can migrate to the adjacent non-chlorine-substituted carbon, while the phenolic hydroxy group attaches to the carbon previously substituted with chlorine, a mechanism known as the NIH shift (shown in Fig. 4.1). Alternatively, the arene oxide may undergo further metabolism by epoxide hydrolase or GST, or may bind with a nucleophilic site on DNA, such as the N7 of guanine, to form an adduct.

As noted above, the chlorine substitution pattern, number of chlorine substituents and presence or absence of unsubstituted 3,4-positions are important factors in determining how readily a particular congener is metabolized by CYP. There are more than 50 isoforms of CYP in humans, and a similar number in experimental animals (Guengerich, 2008). Studies to date have shown that several human isoforms can biotransform one or more PCB congeners; these include CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CY2C9, CYP2C19, and CYP3A4 (Ariyoshi *et al.*, 1995; McGraw & Waller 2006, 2009; Warner *et al.*, 2009; Yamazaki *et al.*, 2011). Related isoforms usually metabolize the same congeners in rat (Morse *et al.*, 1995; Warner *et al.*, 2009; Wu *et al.*, 2011), mouse (Curran *et al.*, 2011), and other species such as fish (Schlezinger *et al.*, 2000). Studies have suggested that congeners with one or no *ortho*-chlorine substitutent are more likely to be metabolized by CYP1 family isoforms. Although it has not been explicitly demonstrated, CYP1B1 metabolizes many of the same substrates as CYP1A1 and CYP1A2 (Shimada *et al.*, 1997) and may also metabolize congeners with one or no *ortho* chlorine. However, CYP1B1 protein is not constitutively expressed in liver, the major drug-metabolizing tissue, and is generally very low in normal tissues (Murray *et al.*, 2001). Congeners with two or more *ortho*-chlorine substituents are usually metabolized by CYP2A, CYP2B, CYP2C and CYP3A subfamily isoforms. It is not well understood which isoforms are involved in monooxygenation of each known PCB congener. This is partly because of difficulties in studying monooxygenation of some of the congeners in vitro with hepatic microsomes or expressed recombinant individual CYP isoforms. The less chlorinated congeners, which tend to be readily metabolized by CYP, are easily studied in vitro; however, until recently they attracted much less attention than the more highly chlorinated congeners (Espandiari *et al.*, 2004). The difficulty in studying highly chlorinated congeners is that they are very slowly metabolized, and conditions for incubation in vitro are difficult to set up to produce sufficient hydroxylated metabolite for analysis. With increasingly sensitive analytical techniques, this problem can be overcome (Yamazaki *et al.*, 2011). While some early publications claimed that certain congeners did not produce metabolites in particular species (Murk *et al.*, 1994), these congeners were later shown through studies in vivo to produce hydroxylated metabolites (Buckman *et al.*, 2007).

An important determinant of the activity of CYP is whether or not the isoform that metabolizes a particular congener is subject to induction, either through exposure to PCBs or through

exposure to other agents known to induce that form of CYP. For example, many congeners with no or one *ortho* chlorine are metabolized by CYP1A1 or CYP1A2 (Curran *et al.*, 2011), and these congeners, like dioxin, polycyclic aromatic hydrocarbons and some components of tobacco smoke, induce CYP1A1 and CYP1A2 by binding to and activating AhR (Parkinson *et al.*, 1983; Safe, 1993). CYP1B1 is also induced by compounds that bind and activate AhR (Murray *et al.*, 2001). A study in which wildtype and knockout mouse strains were exposed in utero and by lactation to a complex mixture of PCBs showed that mice with poor-affinity AhR and lacking CYP1A2 (*Cyp1a2*$^{(-/-)}$ knockout) had higher concentrations of congeners with no or one *ortho* chlorine in tissues than mice with high-affinity AhR and CYP1A2 (*Cyp1a2*$^{(+/+)}$ wild-type), consistent with low metabolism of these PCB congeners in the knockout mice (Curran *et al.*, 2011). PCBs with two or more *ortho* chlorines and at least one *para* chlorine interact with rat and human CAR and induce CYP2B family isoforms, including CYP2B1 and CYP2B6 in a similar manner to the classic inducer, phenobarbital (Parkinson *et al.*, 1980; Al-Salman & Plant, 2012). Some PCBs with two or more *ortho* chlorines have been shown to bind to the human and rat PXR and to human CAR, resulting in upregulation of CYP3A4 (Waller *et al.*, 1996; Petersen *et al.*, 2007; Al-Salman & Plant 2012). CYP3A4 converts PCB-101 and PCB-118 to hydroxylated metabolites (McGraw & Waller, 2009). Activation of CAR also results in upregulation of CYP2B isoforms, several of which have been shown to metabolize PCBs with two or more *ortho* chlorines. For example, human CYP2B6 and the related enzyme, canine CYP2B11, were shown to convert PCB-153 to the 3-hydroxylated metabolite, albeit very slowly (Ariyoshi *et al.*, 1995).

An interesting subgroup of PCBs comprises the 19 chiral PCB congeners, all of which have three or more *ortho* chlorines, which limit rotation around the biphenyl bond. There was evidence that these compounds are enantioselectively metabolized, resulting in depletion of one enantiomer through metabolism, while the form that is resistant to metabolism accumulates (Kania-Korwel *et al.*, 2008; Lehmler *et al.*, 2010). Forms of CYP identified as metabolizing chiral PCBs are rat CYP2B1 and human CYP2B6. For example, there was evidence that PCB-45, PCB-84, PCB-91, PCB-95, PCB-132 and PCB-136 were enantioselectively metabolized to hydroxylated metabolites in vitro by purified rat CYP2B1 and human CYP2B6, leading to alterations in the enantiomeric fractions of the parent congeners (Warner *et al.*, 2009). The positions of hydroxylation were not identified. In a separate study, rat liver microsomes preferentially metabolized (+)-2,2′,3,3′,6,6′-hexachlorobiphenyl (PCB-136) to 5-hydroxy-PCB-136 (5-OH-PCB-136), and treatment of rats with phenobarbital, which induces CYP2B1, further increased the formation of 5-OH-PCB-136 from (+)-PCB-136, compared with untreated rats, thereby leaving an excess of the less readily metabolized (–)-PCB-136 (enantiomeric enrichment) (Wu *et al.*, 2011). There was also a slight increase in 5-OH-PCB-136 formation in dexamethasone-treated rats, which have induced CYP3A, compared with controls. The minor metabolites, 4-OH-PCB-136 and 4,5-dihydroxy-PCB-136 were also formed preferentially by microsomes from phenobarbital-treated rats compared with controls. Since the ryanodine receptor is sensitized only by (–)-PCB-136, more rapid metabolism of (+)-PCB-136 means that the more toxic enantiomer is preferentially retained in the body.

Once formed, OH-PCBs are sometimes further hydroxylated by CYP and perhaps other oxygenases to dihydroxy-PCBs (McLean *et al.*, 1996a; Garner *et al.*, 1999; Wu *et al.*, 2011). If the two OH groups are *ortho* to each other, the metabolites are termed catechols (Garner *et al.*, 1999), and if the two OH groups are *para* to each other, the metabolites are termed hydroquinones (or semiquinones) (Fig. 4.2).

(b) Other oxidative enzymes

PCB catechols and hydroquinones can undergo oxidation to PCB quinones, which are electrophilic, potentially reactive, metabolites. One pathway for quinone formation is through the action of prostaglandin endoperoxide H synthase, an enzyme expressed in extrahepatic tissues, including prostate, ovary, and breast (Wangpradit *et al.*, 2009). Hydroquinones can also be converted to quinones by peroxidases such as horseradish peroxidase, myeloperoxidase, and lactoperoxidase (Srinivasan *et al.*, 2002).

(c) Epoxide hydrolase

If not quickly rearranged to form a phenolic metabolite, an arene oxide metabolite can be converted to a dihydrodiol by addition of water, in a reaction catalysed by epoxide hydrolase (Ota & Hammock, 1980). The dihydrodiol metabolite is generally non-toxic and readily eliminated as the dihydrodiol or as a glucuronide conjugate. It has been suggested that dihydrodiol metabolites of PCBs may be oxidized by dihydrodiol dehydrogenase to the corresponding catechol metabolite, thereby restoring aromaticity to the ring (Garner *et al.*, 1999). Furthermore, catechols could be converted to the *ortho* quinone, which is chemically reactive and can bind to protein and DNA (Zhao *et al.*, 2004).

(d) PCB oxygenation and formation of ROS

PCB biotransformation by CYP can sometimes give rise to formation of reactive oxygen species (ROS) of PCBs, through uncoupling of the CYP cycle. Formation of ROS during PCB monooxygenation by CYP most likely occurs if the congener binds to the CYP substrate-binding site in an orientation that is not favourable for rapid monooxygenation: this has been demonstrated for PCB-77 biotransformation by CYP1A from fish and other vertebrates (Schlezinger *et al.*, 1999, 2000). PCB-77 has been shown to inhibit ethoxyresorufin *O*-deethylase (EROD) activity at high concentrations, perhaps by competitive inhibition of CYP1A by PCB-77 (Hahn *et al.*, 1993). Formation of ROS through uncoupling of the CYP1A cycle has been demonstrated with two other non-*ortho*-substituted PCB congeners, PCB-126 and PCB-169 (Schlezinger *et al.*, 2006). PCB-126 and PCB-169 were also shown to uncouple human CYP1B1 and produce ROS (Green *et al.*, 2008). Since CYP1B1 is expressed and inducible in tissues that are frequent targets for cancer, including colon, breast, lung, endometrium, ovary, and prostate, formation of ROS in these tissues could result in genotoxicity.

PCB metabolism by peroxidases and prostaglandin H synthase (also called cyclooxygenase; COX) can also give rise to ROS (Gonçalves *et al.*, 2009). Another pathway leading to ROS production during PCB metabolism occurs when quinone metabolites are formed. Quinones undergo redox cycling through reaction with glutathione (GSH) to form adducts through Michael addition. The quinone-GSH-adduct can be converted back to the semi-quinone or catechol and recycled through this pathway (Amaro *et al.* 1996; Oakley *et al.*, 1996a). This cycling results in depletion of the important cellular antioxidant, GSH, which can cause oxidative stress to the cell and formation of ROS. Redox cycling of the 2′,5′-dihydroxy metabolite of PCB-12 has been shown to result in DNA adducts through formation of ROS (Oakley *et al.*, 1996a).

(e) GST

Arene oxide metabolites of PCBs are potential substrates for GSTs, as shown in Fig. 4.1. After initial formation of a conjugate with GSH, the two terminal amino acids of the tripeptide are enzymatically removed, leaving a cysteine conjugate of the PCB. This metabolite may be converted to a mercapturic acid, which is readily excreted in urine or bile (Bakke *et al.*, 1982). Alternatively, the cysteine conjugate may be a substrate for cysteine conjugate β-lyase, which converts the cysteine conjugate to a thiol. The

thiol metabolite of the PCB can then be methylated by methyltransferase and oxidized by flavin monooxygenase or CYP to yield the $MeSO_2$-PCB (Mio & Sumino 1985). Depending on its structure, the $MeSO_2$-PCB metabolite may not be readily excreted and may accumulate in tissues, particularly liver, lung, and adipose tissue (Haraguchi *et al.*, 1997a, b; Guvenius *et al.*, 2002; Hovander *et al.*, 2006; Karásek *et al.*, 2007). Chiral PCBs were shown, by analysis of the $MeSO_2$-PCBs present in human adipose tissue, seal blubber and pelican muscle, to form $MeSO_2$-PCBs in an enantioselective manner (Karásek *et al.*, 2007). Tissue accumulation can occur in fatty tissues because the $MeSO_2$-PCBs are very lipid soluble, especially those that are highly chlorinated. Accumulation in lung appears to be due to specific binding of the $MeSO_2$-PCBs to an uteroglobin-like protein/PCB-binding protein, a protein that is synthesized in non-ciliated bronchiolar Clara cells of the lung epithelium (Nordlund-Möller *et al.*, 1990; Anderson *et al.*, 1993). Formation of $MeSO_2$-PCBs and their retention in tissues are of concern because several of these metabolites have been shown to interact with the glucocorticoid receptor (Johansson *et al.*, 1998), and to be antiestrogenic (Letcher *et al.*, 2002). Some $MeSO_2$-PCBs such as 3-$MeSO_2$-2,2′,4′,5-tetrachlorobiphenyl [3′-$MeSO_2$-PCB-49] and 3-$MeSO_2$-2,2′,4′,5,5′-pentachlorobiphenyl [3′-$MeSO_2$-PCB-101] were potent inducers of CYP2B1 and CYP2B2 in rats (Kato *et al.*, 1997).

(f) Glucuronosyltransferase and sulfotransferase

OH-PCBs may be expected to be conjugated with glucuronic acid or sulfate to form non-toxic, readily excreted metabolites, in reactions catalysed by uridine 5′-diphosphate-(UDP)-glucuronosyl transferase (UGT) or 3′-phosphoadenosine-5′-phosphosulfate (PAPS)-sulfotransferase (SULT). Glucuronide and sulfate conjugates of a hydroxylated metabolite of PCB-3 were identified in urine of rabbits given 1 g by gavage (Block & Cornish, 1959).

Studies of glucuronidation have not been conducted with human liver microsomes or UGTs; however, two studies demonstrated formation of glucuronide conjugates with several OH-PCB metabolites, using rat liver microsomes and expressed rat UGTs in yeast strain AH22 (Tampal *et al.*, 2002; Daidoji *et al.*, 2005). In a further study of OH-PCB glucuronidation, it was noted that rates of conjugation varied with the particular OH-PCB substitution pattern, in catfish as well as in rats (Sacco *et al.*, 2008). Those OH-PCBs with only one chlorine flanking a 4-OH group exhibited a higher V_{max} for glucuronidation than OH-PCBs with a 4-OH-3,5-dichloro substitution pattern. The more slowly glucuronidated 4-OH-3,5-dichloro-substituted OH-PCBs were shown to be more potent inhibitors of human estrogen sulfotransferase (human SULT1E1) than those lacking two flanking chlorine atoms (Kester *et al.*, 2000).

In addition to a study in rabbits, which were shown to excrete glucuronide and sulfate conjugates of OH-PCB-3 (Block & Cornish, 1959), further evidence that OH-PCBs are sulfonated in vivo was provided by a study of the fate of PCB-3 in male rats given a dose of 112 mg/kg bw by intraperitoneal injection (Dhakal *et al.*, 2012). The major metabolite was the 4′-sulfate of PCB-3, with little evidence for the glucuronide conjugate; 4′-OH-PCB-3 was converted to the 4′-sulfate conjugate by rat SULT1A1 (Liu *et al.*, 2009). The 4′-OH-PCB-3 was also a substrate for human hepatic cytosolic SULT1A1 (Wang *et al.*, 2006). Other OH-PCBs tested were very poor substrates for human SULT1A1 (Wang *et al.*, 2006), human SULT2A1 (Liu *et al.*, 2006; Ekuase *et al.*, 2011), rat liver SULT1A1, or rat liver SULT2A3 (Liu *et al.*, 2009).

As noted above, OH-PCBs with a 4-OH-3,5-dichloro- structural motif are potent inhibitors of human SULT1E1, with 17-β-estradiol as substrate (Kester *et al.*, 2000). Recent studies showed that some OH-PCBs inhibit sulfonation of dehydroepiandrosterone (DHEA), catalysed by human SULT2A1 or rat SULT2A3 (Liu

et al., 2006, 2009; Ekuase et al., 2011). As well as inhibiting sulfonation of estradiol and DHEA, OH-PCBs inhibit sulfonation and glucuronidation of xenobiotic substrates. Several OH-PCBs were potent inhibitors (low μM values for IC_{50}, the concentration producing 50% inhibition) of sulfonation of 3-hydroxy-benzo[*a*]pyrene catalysed by human liver cytosol, human SULT1A1 and human SULT1E1, but were very weak inhibitors or did not inhibit SULT1A3 (Wang et al., 2005).

(g) Sites of metabolism

For most xenobiotics, including PCBs, the liver is the major organ of metabolism, as most of the drug-metabolizing enzymes are expressed in liver in high concentrations. This is true for several isoforms of CYP, epoxide hydrolase, GST, glucuronosyltransferase, and sulfotransferase; however, the liver is not the only site where these enzymes are expressed. The intestine expresses many of the same enzymes as the liver. The liver is able to convert PCBs to reactive metabolites, and to respond to PCBs that interact with AhR, but the role of metabolism in other tissues is not always clear. Tissues where there are associations between PCB exposure and cancer include the liver, lung, oral mucosa, uterus, thyroid, pancreas, adrenal, breast, skin, blood and lymphatic system, and these effects in some instances may be due to tissue distribution of PCBs or metabolite. As noted above, CYP1B1 is inducible by AhR agonists and has been shown to be expressed in colon, breast, lung, endometrium, ovary and prostate (Schmidt & Bradfield, 1996; Green et al., 2008). Prostaglandin endoperoxide H synthase, implicated in formation of quinone metabolites from OH-PCBs, is expressed in high concentrations in the prostate gland, and is also found in ovary and breast (Wangpradit et al., 2009). The skin contains inducible CYP1A, as well as other drug-metabolizing enzymes (Costa et al., 2010).

4.1.4 Excretion

(a) Humans

Two well designed studies (taking into account ongoing exposure and body weight changes, and not limited by small sample size or short sampling interval) showed that highly chlorinated congeners persist in the body, with half-lives averaging about 8–15 years, while less chlorinated PCBs clearly have shorter half-lives (Table 4.1; Grandjean et al., 2008; Ritter et al., 2011).

Few studies on the faecal (Schlummer et al., 1998; Moser & McLachlan, 2001), or urinary excretion (Price et al., 1972; ATSDR, 2000) of PCBs in humans have been published. A substantial part of absorbed or retained PCBs may be eliminated via breast milk (see Section 1.4 in this *Monograph*). Concentrations varying from 9 to 1915 ng/g lipid have been reported in the general population. Not only parent compounds, but also OH-PCBs were detected in breast milk. Traces of OH-PCBs (median of the sum of 12 congeners, 3 pg/g milk) were found in milk samples collected in 2000–2001 from 15 mothers living in Stockholm; the ratio of total PCBs to total OH-PCBs was approximately 1400, and the major metabolite was an unresolved mixture of 4-OH-CB-107 [4-OH-2,3,3′,4′,5-pentaCB; 4-OH-PCB-109] and 4′-OH-CB-108 [4′-OH-2,3,3′,4,5′-pentaCB; 4-OH-PCB-107] (Guvenius et al., 2003). Adenugba et al. (2009) analysed 15 samples of human bile, collected endoscopically, for seven PCB congeners (PCB-28, PCB-52, PCB-101, PCB-118, PCB-153, PCB-138, and PCB-180). Total PCB concentrations in bile ranged from 6 to 49 ng/mL, and PCB-28 was the predominant congener.

(b) Experimental systems

Elimination half-lives have been estimated in different animal species. In rats, elimination half-lives vary from days (di- and trichlorobiphenyl) to more than 3 months (penta- and

Table 4.1 Estimated human elimination half-lives for nine PCB congeners at background concentrations

Age group	Elimination half-life (years)								
	PCB-28	PCB-52	PCB-105	PCB-118	PCB-138	PCB-153	PCB-170	PCB-180	PCB-187
Children[a]	NR	NR	5.4	5.7	3.7	8.4	7.6	9.1	8
Adults[b]	5.5	2.6	5.2	9.3	10.8	14.4	15.5	11.5	10.5

[a] Grandjean *et al.* (2008), $n = 200$
[b] Ritter *et al.* (2011), $n = 229$
NR, not reported
Adapted from Ritter *et al.* (2011)

hexachlorobiphenyl), while a half-life of approximately 10 months was estimated for Aroclor 1254 in weanling pigs (ATSDR, 2000). Half-lives of a group of congeners (PCB-105, PCB-118, PCB-128, PCB-138, PCB-153, PCB-156, PCB-157, PCB-180, PCB-183) were estimated in monkeys dosed with Aroclor 1254. On average, half-lives varied from 0.4 years (PCB-105) to 1.9 years (PCB-128); however, a wide range of estimates (0.42–7.58 years, depending on individuals) was reported for PCB-128 (Mes *et al.*, 1995b). [These data indicated that PCB half-lives vary according to species, and that PCB half-lives are longer in humans than in experimental animals, including monkeys.]

In rodents, PCBs administered by different routes are mainly excreted in the faeces, with urine usually representing a minor route of excretion.

PCB metabolites that have been identified in urine are mentioned in Section 4.1.3. In addition to OH-PCBs and dihydroxylated PCBs and corresponding glucuronides also observed in other studies, the elimination in urine of sulfated metabolites of PCB-3, PCB-3 2′-sulfate, PCB-3 3′-sulfate, and PCB-3 4′-sulfate after a single intraperitoneal dose of PCB-3 (112 mg/kg bw) was reported. In rats, approximately 3% of the administered dose was excreted in the urine as sulfates over 36 hours, with peak excretion occurring 10–20 hours after exposure (Dhakal *et al.*, 2012). Mercapturic acid of [^{14}C]-2,4′,5-trichlorobiphenyl (PCB-31) was isolated from the urine of rats treated with this congener (Bakke *et al.*, 1982). This metabolite represented 0.3% of the administered dose of 4 mg per rat. About 57% of the administered dose was excreted in the bile, and 30–35% was present as metabolites in the mercapturic acid pathway.

Lactation is also a major route of excretion of PCBs in animals. In monkeys exposed to different doses of Aroclor 1254 in long-term studies, approximately 4% of the intake was eliminated in milk (Mes *et al.*, 1994). The transfer of [^{14}C]-labelled congeners PCB-77, PCB-126, PCB-169, and PCB-105 to milk has been investigated in mice (Sinjari *et al.*, 1996). These compounds were administered intraperitoneally to lactating mice at a single dose of 2.0 µmol/kg bw each on postnatal day 11. Concentrations of PCB-126, PCB-169 and PCB-105 in milk 1 day after administration were higher (1450–2520 pmol/mL) than concentrations of PCB-77 (580 pmol/mL).

In addition to these routes of elimination, other minor pathways have been reported. Studies by Yoshimura & Yamamoto (1975) on PCB-66 in rats have suggested that excretion of unmetabolized PCB through the small intestinal wall may occur. In other experiments with rats, PCBs were excreted unchanged in hair and through the skin (Matthews *et al.*, 1976).

4.2 Genetic and related effects

Since the first *IARC Monograph* on PCBs (IARC, 1978), the genetic and related effects of PCBs have been studied in several experimental systems and in humans (for details and references, see Tables 4.2, 4.3, 4.4, 4.5, 4.6), and summarized in numerous reviews (Safe, 1989; Silberhorn *et al.*, 1990; ATSDR, 2000; Ludewig, 2001).

4.2.1 Exposed humans

Several studies have used cytogenetic effects (structural chromosome aberration, sister-chromatid exchange, and DNA adducts) in cells from body fluids (blood and semen) as biomarkers in humans occupationally or environmentally exposed to PCBs (see Table 4.2).

(a) Genotoxicity and cytogenicity from occupational exposure

Peripheral lymphocytes from 32 workers exposed occupationally to commercial PCB mixtures (DELOR 103 and 106) for up to 25 years were examined for cytogenetic changes. All workers with PCB exposure were smokers and moderate drinkers, and control groups were chosen accordingly: control group 1 consisted of 20 people working outside the PCB-production unit, and control group 2 consisted of 20 employees from administrative offices and the research department (Kalina *et al.*, 1991). Workers with PCB exposure were also exposed to formaldehyde and benzene, but at levels not exceeding national exposure limits. Occupational exposure to PCB mixtures led to an increase in PCB plasma concentrations of more than 100-fold (305–487 µg/L), when compared with the control groups (1.5–3 µg/L). A significant increase in the frequency of chromosomal aberration and sister-chromatid exchange was observed in workers exposed to PCBs for at least 11 years; however, no dose–response effect was observed between cytogenetic effects and PCB blood concentrations. [The Working Group was not able to determine how the PCB plasma concentrations were measured. No quantitative data were provided on the exposure of the workers to benzene and formaldehyde, or on whether all three groups were similarly exposed to benzene and formaldehyde. The choice of control group used for the *t*-test analysis was not clearly indicated].

An increase in structural chromosomal aberration in lymphocytes was also observed in workers occupationally exposed to PCBs when compared with a non-exposed control group; however, no information on PCB blood concentrations or confounders was available (Joksić & Marković, 1992).

Peripheral blood lymphocytes from male workers (n = 21) exposed occupationally to PCBs for 2–5 years at a factory decontaminating industrial transformers and capacitors and from workers in an industrial control group (87; 53 men and 34 women) were analysed for structural and numerical chromosomal aberrations. Significant increases of twofold in the frequency of structural chromosomal aberration and four- to sixfold in the frequency of premature centromere division in mitotic chromosomes were observed in the PCB-exposed group (Jakab *et al.*, 1995; Major *et al.*, 1999). [The Working Group noted that PCB concentrations in blood and/or air were not monitored, the industrial control group was not further specified, and no adjustment for confounders was made.]

Two studies of occupational exposure examined workers exposed to PCBs after a fire at an electric station (Elo *et al.*, 1985; Melino *et al.*, 1992). In one study, maximum blood PCB concentrations (median, 14 µg/L) were reached 3 days after exposure and declined over the course of 1 month to background levels (≤ 2 µg/L). No exposure-related increases in the frequency of structural chromosomal aberration and sister-chromatid exchange in 15 PCB-exposed workers were observed for

Table 4.2 Genetic effects and markers of oxidative DNA damage in humans exposed to PCBs

Target tissue	End-point	Result	Comments	Reference
Occupational exposure				
Peripheral blood lymphocytes	Chromosomal aberration Sister-chromatid exchange	– –	Exposed, 15; unexposed, not defined No details on individual numbers and statistical analysis	Elo *et al.* (1985)
Peripheral blood lymphocytes	Chromosomal aberration	–	Exposed, 45 (29 men, 12 women, 4 children) living within 2 km from capacitor-manufacturing plant (24 workers, 21 residents); unexposed; pre-employment test from workers Heavy smokers excluded; no statistical analysis; no correlation with PCB concentrations (11 congeners) in blood and adipose tissue [no details on PCB concentrations were given]	Tretjak *et al.* (1990)
Peripheral blood lymphocytes	Chromosomal aberration Sister-chromatid exchange	+ ($P < 0.01$) + ($P < 0.05$)	Exposed to technical PCB mixture, 32; unexposed group 1 (working outside production unit), 20; unexposed group 2 (administration and research), 20. Positive correlation with duration of exposure but not blood PCB levels	Kalina *et al.* (1991)
Peripheral blood lymphocytes	Chromosomal aberration Micronucleus formation Sister-chromatid exchange	? + +	Exposed, 48; unexposed, 15 No statistical analysis performed	Joksić & Marković (1992)
Peripheral blood lymphocytes	Chromosomal aberration Sister-chromatid exchange	– –	Exposed, 12; unexposed, 19 No serum PCB concentrations; both groups contained moderate smokers; no confounder taken into account	Melino *et al.* (1992)
Peripheral blood lymphocytes	Chromosomal aberration Premature centromere division	+ ($P < 0.01$) + ($P < 0.01$)	Exposed, 21 (men); unexposed, 87 (53 men,34 women) Heavy smokers (> 20 cigarettes/day); heavy drinkers (> 100 g alcohol/day); donors with neoplasia	Jakab *et al.* (1995), Major *et al.* (1999)
Urine	Oxidative DNA damage (8-OHdG)	–	Study cohort: 64; pre- and post-shift workplace exposure	Wen *et al.* (2008)
Environmental exposure				
Peripheral blood lymphocytes	Chromosomal aberration	–	Exposed, 36 (Yucheng; 17 men, 19 women); unexposed 10 (5 men, 5 women) Sampling of exposed group occurred 3 years after exposure; chromosomal aberrations included breaks, exchanges, acentric fragments, and gaps.	Wuu & Wong (1985)
Peripheral blood lymphocytes	Chromosomal aberration Sister-chromatid exchange *After exposure of lymphocytes to α-naphthoflavone* in vitro*:* Chromosomal aberration Sister-chromatid exchange	– – – + ($P < 0.001$)	Exposed, 35 women (Yucheng victims); unexposed, 24 Blood samples of exposed individuals were taken in 1985 or 5 years after the exposure had occurred; unexposed women were from the same county; all participants were nonsmokers	Lundgren *et al.* (1988)

Table 4.2 (continued)

Target tissue	End-point	Result	Comments	Reference
Peripheral blood lymphocytes	Sister-chromatid exchange	–	Exposed, 16 Yusho patients; unexposed, 39	Nagayama *et al.* (2001)
	Sister-chromatid exchange after exposure of lymphocytes to α-naphthoflavone	–		
Peripheral blood lymphocytes	Micronucleus formation	+ ($P < 0.01$; PCB-118)	Study cohort: up to 1583; age 50–65 years; confounder: age, sex, smoking, lifestyle, body mass index	De Coster *et al.* (2008)
	DNA damage (comet assay)	+ ($P < 0.05$; PCB-118)		
Blood serum	Prostate specific antigen	–		
	Carcinoembryogenic antigen	–		
	TP53	+ ($P < 0.05$; sum of PCB-138, PCB-153, PCB-180)		
Leukocytes	DNA adduct	–	Study cohort: 103 Inuits, categorized into low (1.7–20 µg/L; $n = 54$), medium (21–40 µg/L; $n = 21$) and high (41–143 µg/L; $n = 28$) PCB exposure	Ravoori *et al.* (2008)
Leukocytes	DNA adduct	Negative correlation with PCB ($P < 0.0001$)	Study cohort: 83 Inuits: 56 women, 27 men Effect of age, sex, smoking status, PCB and selenium concentrations on DNA adduct accumulation taken into account	Ravoori *et al.* (2010)
	DNA adduct and 8-OHdG	Negative correlation in the high selenium/PCB ratio group ($P < 0.01$ and $P = 0.014$; respectively)		
Sperm	XY disomy	+ ($P < 0.001$)	Study cohort: 192 men from subfertile couples	McAuliffe *et al.* (2012)
	Total sex-chromosome disomy	+ ($P < 0.001$)		
	XX disomy	Negative correlation ($P < 0.001$)		
Sperm	Sperm chromatid structure	+ ($P < 0.01$)	Study cohort: 176 adult men (Swedish)	Rignell-Hydbom *et al.* (2005)
Sperm	Sperm chromatid structure (DNA fragmentation)	+	Study cohort: 707 adult men (193 Greenland Inuits, 178 Swedish, 141 Polish, and 195 Ukrainian) Statistically positive association for Ukranian and Swedish cohorts, and for European cohorts combined (Sweden, Poland, Ukraine)	Spanò *et al.* (2005)
Sperm	Sperm chromatid structure (DNA fragmentation)	+ ($P < 0.05$)	Study cohort: 652 adult men (200 Greenland Inuits; 166 Swedish, 134 Polish, and 152 Ukrainian) Significant association only for European cohorts combined (Sweden, Poland, Ukraine)	Stronati *et al.* (2006)
Urine	Oxidative DNA damage (8-OHdG)	–	Study cohort: up to 1583; age 50–65 years; confounder: age, sex, smoking, lifestyle, body mass index	De Coster *et al.* (2008)

8-OHdG, 8-hydroxy-2′-deoxyguanosine

Table 4.3 Genetic and related effects of commercial PCB mixtures in experimental systems in vitro

Agent	Test system	Results[a]		Dose[b] (LED or HID), µg/mL	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
Non-mammalian systems					
Aroclor 1221	*Salmonella typhimurium* TA1538, reverse mutation	–	(+)	200	Wyndham *et al.* (1976)
	Saccharomyces cerevisiae, strain RS112, interchromosomal recombination	+	+	10 000	Schiestl *et al.* (1997)
	Salmonella typhimurium TA98, TA1538, reverse mutation	–		5000 µg/plate	Shahin *et al.* (1979)
Aroclor 1254	*Salmonella typhimurium* C3076, D3052, G46, TA98, TA1000, TA1535, TA1537, TA1538, and *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	NR	Probst *et al.* (1981)
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, reverse mutation	–	–	500	Bruce & Heddle (1979) Schoeny *et al.* (1979)
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	333	Dunkel *et al.* (1984)
	Salmonella typhimurium TA1538, reverse mutation	–	–	200	Wyndham *et al.* (1976)
	Salmonella typhimurium TA98, TA100, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	200 µg/plate	Evandri *et al.* (2003)
	Saccharomyces cerevisae, heterozygous transgenic for human MS32 minisatellite, length mutation	+	NR	6000	Appelgren *et al.* (1999)
Aroclor 1260	*Saccharomyces cerevisiae*, strain RS112, interchromosomal recombination	+	+	15 000	Schiestl *et al.* (1997)
Aroclor 1268	*Salmonella typhimurium* TA1538, reverse mutation	–	–	200	Wyndham *et al.* (1976)
Kanechlor 300	*Salmonella typhimurium* TA1535, TA1536, TA1537, TA1538, TA98, TA100, reverse mutation	–	–	NR	Odashima (1976)
	Salmonella typhimurium TA98, TA100, *Escherichia coli* WP2, reverse mutation	–	–	NR	Sugimura *et al.* (1976)
Kanechlor 500	*Salmonella typhimurium* TA1535, TA1536, TA1537, TA1538, TA98, TA100, reverse mutation	–	–	NR	Odashima (1976)
	Salmonella typhimurium TA98, TA100, *Escherichia coli* WP2, reverse mutation	–	–	NR	Sugimura *et al.* (1976)
Clophen 30	*Drosophila melanogaster*, genetic crossing-over, sex-chromosome loss	–		250	Nilsson & Ramel (1974)
Clophen 50	*Drosophila melanogaster*, genetic crossing-over, sex-chromosome loss	–		200	Nilsson & Ramel (1974)
Mammalian cells in vitro					
Aroclor 1221	Intrachromosomal (non-homologous) recombination at *Hprt* locus, Chinese hamster lung Sp5/V79 cells	–		30	Helleday *et al.* (1998)
	Intrachromosomal (homologous) recombination *Hprt* locus, Chinese hamster lung SPD8/V79 cells	+		20	

Table 4.3 (continued)

Agent	Test system	Results[a]		Dose[b] (LED or HID), µg/mL	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
Aroclor 1221 (cont.)	Intrachromosomal recombination by deletion in *HPRT* locus, human lymphoblastoid GM6804 cells	+		5	Aubrecht *et al.* (1995)
Aroclor 1016	DNA adducts ^{32}P-postlabelling, primary human hepatocytes (three donors)	(+)		23	Borlak *et al.* (2003)
Aroclor 1242	Gene mutation (ouabain resistance), Chinese hamster fibroblast V79 cells	–		150	Hattula (1985)
	Chromosomal aberrations, chicken embryo (*Gallus domesticus*)	–		20	Blazak & Marcum (1975)
Aroclor 1254	DNA single-strand breaks, alkaline elution, rat hepatocytes	+		100	Sina *et al.* (1983)
	DNA strand breaks (comet assay), rat primary prostate cells	+		1	Cillo *et al.* (2007)
	Unscheduled DNA synthesis, primary rat hepatocytes	+		20 (MED)	Althaus *et al.* (1982)
	Unscheduled DNA synthesis, primary F344 rat hepatocytes	–		[16] 50 µM	Probst *et al.* (1981)
	DNA adducts ^{32}P-postlabelling, primary fetal rat hepatocytes		–	[16] 50 µM	Dubois *et al.* (1995)
	DNA adducts ^{32}P-postlabelling, human hepatocarcinoma HepG2 cells	–		[16] 50 µM	Dubois *et al.* (1995)
	DNA adducts ^{32}P-postlabelling, primary human hepatocytes (three donors)	(+)		[20] 60 µM	Borlak *et al.* (2003)
	Detection of repairable adducts by growth inhibition (DRAG) assay in wildtype and DNA repair-deficient Chinese hamster ovary cells	–		135/114, 127, 132[c]	Johansson *et al.* (2004)
	Micronucleus formation, human keratinocytes	–		3	van Pelt *et al.* (1991)
	Chromosomal aberrations, human lymphocytes (five donors)	+		0.1	Sargent *et al.* (1989)
	Cell transformation, Syrian hamster embryo cells	–		50	Pienta (1980)
Clophen A60	Gene mutation (ouabain resistance), Chinese hamster fibroblast V79 cells	–		150	Hattula (1985)
Kanechlor 500 + 600 (plus PCDD/PCDF/ PCB-77, PCB-126, PCB-169 as 0.5% wt)	Sister-chromatid exchange, human lymphocytes	+	+	[0.4 ng WHO-TEQ/g; 0.25 ng WHO-TEQ/g]	Nagayama *et al.* (1994)

[a] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an inadequate study)

[b] Approximately minimal lethal dose not reported.

[c] Dose 135 µg/mL is the IC_{50} concentration inhibiting growth of wildtype CHO cells (AA8) by 50%; doses 114, 127 and 132 µg/mL are the IC_{50} for repair-deficient CHO cells EM9, UV4 and UV5, respectively.

HID, highest effective dose; LED, lowest effective dose; MED, maximum effective dose; PCDD/PCDF, polychlorinated dibenzodioxin/polychlorinated dibenzofuran; TEQ, toxic equivalency

Table 4.4 Genetic and related effects of commercial PCB mixtures in experimental animals in vivo

Agent	Test system	Results[a]	Dose[b] (LED or HID)	Reference
Aroclor 1221	Intrachromosomal recombination by DNA deletion, homozygous C57BL/6J p^{un}/p^{un} mouse	+	1000 ip × 1	Schiestl *et al.* (1997)
Aroclor 1242	DNA adducts ^{32}P-postlabelling, and 8-OHdG, HPLC/ECD-analysis, male Lewis rat liver, thymus, glandular stomach, spleen, testes, seminal vesicles and prostate gland	–	20 po × 1	Schilderman *et al.* (2000)
	Chromosomal aberrations (structural), male Osborne-Mendel rat bone-marrow and spermatogonial cells	–	5000 po × 1	Green *et al.* (1975a)
		–	500 po × 4	
	Dominant lethality, Osborne-Mendel rat	–	2500 po × 1	Green *et al.* (1975b)
		–	250 po × 5	
Aroclor 1254	DNA adducts (I-compounds only) ^{32}P-postlabelling, male Sprague-Dawley rat liver, kidney, lung	–	500 ip × 2	Nath *et al.* (1991)
	DNA adducts ^{32}P-postlabelling, male F344 rat liver	–	25 po × 35	Chadwick *et al.* (1993)
	Unscheduled DNA synthesis, Sprague-Dawley rat, primary hepatocytes	–	300 ip × 1	Kornbrust & Dietz (1985)
	Unscheduled DNA synthesis, rat, primary hepatocytes	–	500 ip × 1	Shaddock *et al.* (1989)
	Unscheduled DNA synthesis, male cynomolgus monkey, primary hepatocytes	–	50 ip × 1	Hamilton *et al.* (1997)
		–	50 ip × 2	
	Micronucleus formation, fish (*C. carpio*), erythrocytes	+	50 ip × 1	Al-Sabti (1986)
	Micronucleus formation, B6C3F$_1$ mouse, bone-marrow cells	–	15 000 ip × 5	Bruce & Heddle (1979)
	Chromosomal aberrations (structural), fish (*C. carpio; T. tinica; C. idella*), kidney cells	+	50 ip × 1	Al-Sabti (1985)
	Chromosomal aberrations (structural), Sprague-Dawley rat, spermatogonial cells	–	50 po × 7	Dikshith *et al.* (1975)
	Chromosomal aberrations (structural), male Osborne-Mendel rat, bone-marrow cells	–	300 po × 5	Green *et al.* (1975a)
	Chromosomal aberrations (structural), male Holtzman rat, bone-marrow and spermatogonial cells	–	500 ppm, 5 weeks	Garthoff *et al.* (1977)
	Sperm morphology, B6C3F$_1$ mice	–	7500 ip × 5	Bruce & Heddle (1979)
	Germline length mutation PC-1 minisatellite, male C57B1/6 mouse, liver	+	100 ip × 1	Hedenskog *et al.* (1997)
	Germline length mutation PC-2 minisatellite, male C57B1/6 mouse, liver	–	100 ip × 1	Hedenskog *et al.* (1997)
	Dominant lethal mutation, Osborne-Mendel rats	–	300 po × 5	Green *et al.* (1975b)
	Gene mutation, transgenic male BigBlue™ mice	(+)	100 ppm in diet, 7 weeks	Davies *et al.* (2000)
Aroclor 1260	Intrachromosomal recombination by DNA deletion, homozygous C57BL/6J p^{un}/p^{un} mouse	+	500 ip × 1	Schiestl *et al.* (1997)
	DNA adducts ^{32}P-postlabelling, male and female B6C3F$_1$ mouse, liver	–	50 po × 1	Whysner *et al.* (1998)
		–	200 ppm × 2 weeks	

Table 4.4 (continued)

Agent	Test system	Results[a]	Dose[b] (LED or HID)	Reference
Kaneclor 300	Chromosomal aberrations, mouse, bone-marrow cells	–	NR[c]	Odashima (1976)
	Chromosomal aberrations, rat, bone-marrow cells	–	NR[c]	Odashima (1976)
Kaneclor 500	Micronucleus formation, male ddY mice, bone-marrow cells	(+)	100 po × 6	Watanabe *et al.* (1982)
		–	100 sc × 6	
	Chromosomal aberrations, mouse, bone-marrow cells	+	NR	Odashima (1976)
	Chromosomal aberrations, rat, bone-marrow cells	–	NR	Odashima (1976)
Kanechlor [no further specification given]	DNA strand breaks (comet assay), ddY male mouse (stomach, colon, liver, kidney, urinary bladder, lung, brain, bone marrow)	–	1000 po × 1	Sasaki *et al.* (2000)
PCB_3[c]	Micronucleus formation, fish (*Misgurnus anguillicaudatus*), erythrocytes	+	0.5 mg/L × 7 d	Chu *et al.* (1996a)
		+	1 mg/L × 2 d	
		–	10 ppm × 12 mo	

[a] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an inadequate study)

[b] In-vivo tests, mg/kg bw

[c] Commercial PCB mixture manufactured in China, the composition of which was similar to that of Aroclor 1242 (see Section 1.1, Table 1.8)

CB, chlorobiphenyl; d, day; HID, highest effective dose; HPLC/ECD, high-performance liquid chromatography electrochemical detection; ip, intraperitoneal; LED, lowest effective dose; mo, month; NR, not reported; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; po, oral administration; TEQ, toxic equivalency

Table 4.5 Genetic and related effects of PCB congeners and their metabolites in experimental systems in vitro

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]		Dose[c] (LED or HID), µg/mL	Reference
			Without exogenous metabolic system	With exogenous metabolic system		
Non-mammalian systems						
2-MonoCB	PCB-1	*Salmonella typhimurium* C3076, D3052, G46, TA98, TA1000, TA1535, TA1537, TA1538, reverse mutation	–	–	1000	McMahon et al. (1979)
4-MonoCB	PCB-3	*Salmonella typhimurium* C3076, D3052, G46, TA98, TA1000, TA1535, TA1537, TA1538, reverse mutation	–	–	1000	McMahon et al. (1979)
4-MonoCB	PCB-3	*Salmonella typhimurium* TA1538, reverse mutation	?	+	50 µg/plate	Wyndham et al. (1976)
4-MonoCB	PCB-3	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, reverse mutation	–	–	200	Schoeny (1982)
4,4-DiCB	PCB-15	*Salmonella typhimurium* TA98, TA100, reverse mutation	–	–	100	Butterworth et al. (1995)
4,4'-DiCB	PCB-15	*Drosophila melanogaster*, somatic mutation and recombination, eye mosaic test	+	+	223	Butterworth et al. (1995)
2,2',4,4'-TetraCB	PCB-47	*Salmonella typhimurium* TA98, TA100, reverse mutation	–	–	200	Schoeny (1982)
2,2',5,5'-TetraCB	PCB-52	*Salmonella typhimurium* TA1538, reverse mutation	–	–	200 µg/plate	Wyndham et al. (1976)
2,2',5,5'-TetraCB	PCB-52	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, reverse mutation	NT	–	200 µg/plate	Hsia et al. (1978)
4-OH-2,2',5,5'-TetraCB	4-OH-PCB-52	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, reverse mutation	NT	–	20 µg/plate	Hsia et al. (1978)
3,4-Epoxy-2,2',5,5'-tetraCB	3,4-Epoxy-PCB-52	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, reverse mutation	NT	–	200 µg/plate	Hsia et al. (1978)
3,3',4,4'-TetraCB	PCB-77	*Salmonella typhimurium* TA98, TA100, reverse mutation	–	–	200	Schoeny (1982)
2,2',4,4',6,6'-HexaCB	PCB-155	*Salmonella typhimurium* TA98, TA100, reverse mutation	–	–	200	Schoeny (1982)
2,2',3,3',4,4',5,5',6,6'-DecaCB	PCB-209	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	5000	Han et al. (2009)

Table 4.5 (continued)

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]		Dose[c] (LED or HID), µg/mL	Reference
			Without exogenous metabolic system	With exogenous metabolic system		
Mammalian cells in vitro						
2',5'-HQ-2-MonoCB	Metabolite of PCB-1	Polyploidy, Chinese hamster lung V79 cells	–		4.4	Flor & Ludewig (2010)
2',5'-HQ-2-MonoCB	Metabolite of PCB-1	Sister-chromatid exchange, Chinese hamster lung V79 cells	–		4.4	Flor & Ludewig (2010)
2',5'-HQ-3-MonoCB	Metabolite of PCB-2	Polyploidy, Chinese hamster lung V79 cells	+		1.1	Flor & Ludewig (2010)
2',5'-HQ-3-MonoCB	Metabolite of PCB-2	Sister-chromatid exchange, Chinese hamster lung V79 cells	–		2.2	Flor & Ludewig (2010)
4-MonoCB	PCB-3	Binding (covalent) to DNA, RNA or protein, Chinese hamster ovary cells	+		2	Wong et al. (1979)
4-MonoCB	PCB-3	Unscheduled DNA synthesis, Chinese hamster ovary cells	(+)		2	Wong et al. (1979)
4-MonoCB	PCB-3	DNA adducts (^{32}P-postlabelling), primary human hepatocytes (three donors)	+		43	Borlak et al. (2003)
4-MonoCB	PCB-3	Gene mutation, Chinese hamster lung V79 cells, *Hprt* locus	–		56	Zettner et al. (2007)
2'-OH-4-MonoCB	Metabolite of PCB-3		–		20	
3'-OH-4-MonoCB	Metabolite of PCB-3		–		20	
4'-OH-4-MonoCB	Metabolite of PCB-3		–		20	
2',5'-HQ-4-MonoCB	Metabolite of PCB-3		–		1.7	
3',4'-HQ-4-MonoCB	Metabolite of PCB-3		–		5.5	
2',5'-Q-4-MonoCB	Metabolite of PCB-3		+		0.1	
3',4'-Q-4-MonoCB	Metabolite of PCB-3		+		0.1	
4-MonoCB	PCB-3	Micronucleus formation, Chinese hamster lung V79 cells	–		38	Zettner et al. (2007)
2'-OH-4-MonoCB	Metabolite of PCB-3		+		10	
3'-OH-4-MonoCB	Metabolite of PCB-3		+		20	
4'-OH-4-MonoCB	Metabolite of PCB-3		+		15	
2',5'-HQ-4-MonoCB	Metabolite of PCB-3		+		0.6	
3',4'-HQ-4-MonoCB	Metabolite of PCB-3		+		3.3	
2',5'-Q4-MonoCB	Metabolite of PCB-3		+		0.1	
3',4'-Q-4-MonoCB	Metabolite of PCB-3		+		0.5	

Table 4.5 (continued)

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]		Dose[c] (LED or HID), µg/mL	Reference
			Without exogenous metabolic system	With exogenous metabolic system		
4-MonoCB	PCB-3	Aneuploidy, Chinese hamster lung V79 cells	–		38	Zettner et al. (2007)
2'-OH-4-MonoCB	Metabolite of PCB-3		+		10	
3'-OH-4-MonoCB	Metabolite of PCB-3		+		20	
4'-OH-4-MonoCB	Metabolite of PCB-3		+		15	
2',5'-HQ-4-MonoCB	Metabolite of PCB-3		+		0.6	
3',4'-HQ-4-MonoCB	Metabolite of PCB-3		+		3.3	
2',5'-Q-4-MonoCB	Metabolite of PCB-3		+		0.5	
3',4'-Q-4-MonoCB	Metabolite of PCB-3		+		1.1	
2',5'-HQ-4-MonoCB	Metabolite of PCB-3	Polyploidy, Chinese hamster lung V79 cells	+		1.1	Flor & Ludewig (2010)
3',4'-HQ-4- MonoCB	Metabolite of PCB-3	Polyploidy, Chinese hamster lung V79 cells	–		2.2	Flor & Ludewig (2010)
2',5'-HQ-4-MonoCB	Metabolite of PCB-3	Sister-chromatid exchange, Chinese hamster lung V79 cells	–		2.2	Flor & Ludewig (2010)
3',4'-HQ-4-MonoCB	Metabolite of PCB-3	Sister-chromatid exchange, Chinese hamster lung V79 cells	+		1.1	Flor & Ludewig (2010)
2',5'-Q-4-MonoCB	Metabolite of PCB-3	Micronucleus formation, human breast epithelial MCF-10A cells	+		0.1	Venkatesha et al. (2008)
2',5'-Q-4-MonoCB	Metabolite of PCB-3	Micronucleus formation, Chinese hamster lung V79 cells	+		0.6	Jacobus et al. (2008)
2,2',5,5'-TetraCB	PCB-52	DNA strand breaks (alkaline sedimentation), mouse fibroblast L-929 cells	+		20	Stadnicki et al. (1979)
4-OH-/3-OH-2,2',5,5'-TetraCB (4 : 1)	Metabolites of PCB-52	DNA strand breaks (alkaline sedimentation), mouse fibroblast L-929 cells	+		20	Stadnicki et al. (1979)
3,4-Epoxy-2,2',5,5'-TetraCB	Metabolite of PCB-52	DNA strand breaks (alkaline sedimentation), mouse fibroblast L-929 cells	+		10	Stadnicki et al. (1979)
2,2',5,5'-TetraCB	PCB-52	DNA strand breaks (comet assay), human lymphocytes (six donors)	(+)		0.3	Sandal et al. (2008)
2,2',5,5'-TetraCB	PCB-52	Sister-chromatid exchange, human lymphocytes (four donors)	–		1	Sargent et al. (1989)
2,2',5,5'-TetraCB	PCB-52	Chromosomal aberrations, human lymphocytes (5–9 donors)	–		1	Sargent et al. (1989)

Table 4.5 (continued)

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]		Dose[c] (LED or HID), µg/mL	Reference
			Without exogenous metabolic system	With exogenous metabolic system		
2,2',5,5'-TetraCB and 3,3',4,4'-tetraCB	PCB-52 + PCB-77	Chromosomal aberrations, human lymphocytes (5–9 donors)	+		$1 + 10^{-5}$	Sargent et al. (1989)
2,2',5,5'-TetraCB and 3,3',4,4'-tetraCB	PCB-52 + PCB-77	Sister-chromatid exchange, human lymphocytes (four donors) in vitro	–		$1 + 10^{-5}$	Sargent et al. (1989)
3-$MeSO_2$-2',3',4,5-TetraCB	5-$MeSO_2$-PCB-56	Sister-chromatid exchange, human lymphocytes	–		7.1	Nagayama et al. (1999)
3-$MeSO_2$-2',3',4,5-TetraCB	5-$MeSO_2$-PCB-56	Micronucleus formation, human lymphocytes	–		7.1	Nagayama et al. (1995)
3,3',4,4'-TetraCB	PCB-77	DNA strand breaks (comet assay), human lymphocytes (three donors)	–		25	Belpaeme et al. (1996a)
3,3',4,4'-TetraCB	PCB-77	DNA strand breaks (comet assay), human lymphocytes (six donors)	(+)		3	Sandal et al. (2008)
3,3',4,4'-TetraCB	PCB-77	DNA adducts ^{32}P-postlabelling, human hepatocarcinoma HepG2 cells	+		15	Dubois et al. (1995)
3,3',4,4'-TetraCB	PCB-77	DNA adducts ^{32}P-postlabelling, primary fetal rat hepatocytes		+	15	Dubois et al. (1995)
3,3',4,4'-TetraCB	PCB-77	Sister-chromatid exchange, human lymphocytes (four donors) in vitro	–		0.1	Sargent et al. (1989)
2,2',5,5'-TetraCB and 3,3',4,4'-tetraCB	PCB-52 + PCB-77	Sister-chromatid exchange, human lymphocytes (four donors) in vitro	–		$1 + 10^{-5}$	Sargent et al. (1989)
3,3',4,4'-TetraCB	PCB-77	Micronucleus formation, human lymphocytes (two donors)	–		500	Belpaeme et al. (1996a)
3,3',4,4'-TetraCB	PCB-77	Chromosomal aberrations (structural), human lymphocytes (5–9 donors)	+		0.01	Sargent et al. (1989)
3-$MeSO_2$-3',4,4',5-TetraCB	5-$MeSO_2$-PCB-77	Sister-chromatid exchange, human lymphocytes	–		6.8	Nagayama et al. (1999)
3-$MeSO_2$-3',4,4',5-TetraCB	5-$MeSO_2$-PCB-77	Micronucleus formation, human lymphocytes	–		7.8	Nagayama et al. (1995)
4,4'-$(OH)_2$-3,3',5,5'-TetraCB	Metabolite of PCB-80	Detection of repairable adducts by growth inhibition (DRAG) assay in wildtype and DNA repair-deficient Chinese hamster ovary cells	(+)		140/102, 92, 91[d]	Johansson et al. (2004)
4-$MeSO_2$-2,2',3',4',5-PentaCB	4'-$MeSO_2$-PCB-87	Sister-chromatid exchange, human lymphocytes	+		5.8	Nagayama et al. (1999)

Table 4.5 (continued)

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]		Dose[c] (LED or HID), µg/mL	Reference
			Without exogenous metabolic system	With exogenous metabolic system		
4-$MeSO_2$-2,2',3',4',5-PentaCB	4'-$MeSO_2$-PCB-87	Micronucleus formation, human lymphocytes	–		5.8	Nagayama et al. (1995)
2,2',4,5,5'-PentaCB	PCB-101	DNA strand breaks (comet assay), fish fibroblast RTG-2 cells	+		16	Marabini et al. (2011)
2,2',4,5,5'-PentaCB	PCB-101	Micronucleus formation, fish fibroblast RTG-2 cells	+		16	Marabini et al. (2011)
3-$MeSO_2$-2,2',4',5,5'-PentaCB	3'-$MeSO_2$-PCB-101	Sister-chromatid exchange, human lymphocytes	+		5.2	Nagayama et al. (1999)
3-$MeSO_2$-2,2',4',5,5'-PentaCB	3'-$MeSO_2$-PCB-101	Micronucleus formation, human lymphocytes	–		5.2	Nagayama et al. (1995)
4-OH-2,3,3',4',5-PentaCB	Metabolite of PCB-109	Detection of repairable adducts by growth inhibition (DRAG) assay in wildtype and DNA repair-deficient Chinese hamster ovary cells	–			Johansson et al. (2004)
2,3',4,4',5-PentaCB	PCB-118	DNA strand breaks (comet assay), fish fibroblast RTG-2 cells	+		10	Marabini et al. (2011)
2,3',4,4',5-PentaCB	PCB-118	Micronucleus formation, fish fibroblast RTG-2 cells	+		10	Marabini et al. (2011)
3,3',4,4',5-PentaCB	PCB-126	Micronucleus formation, human hepatoma HepG2 cells in vitro	–		0.003	Wei et al. (2009b)
2,2',3,4,4',5'-HexaCB	PCB-138	DNA strand breaks (comet assay), fish fibroblast RTG-2 cells	+		25	Marabini et al. (2011)
2,2',3,4,4',5'-HexaCB	PCB-138	Micronucleus formation, fish fibroblast RTG-2 cells	–		25	Marabini et al. (2011)
4-$MeSO_2$-2,2',3',5,5',6'-HexaCB	4'-$MeSO_2$-PCB-151	Sister-chromatid exchange, human lymphocytes	–		9.6	Nagayama et al. (1999)
4-$MeSO_2$-2,2',3',5,5',6'-HexaCB	4'-$MeSO_2$-PCB-151	Micronucleus formation, human lymphocytes	–		9.6	Nagayama et al. (1995)
2,2',4,4'5,5'-HexaCB	PCB-153	Chromosomal aberrations (structural), human lymphocytes (5–9 donors)	+		1	Sargent et al. (1989)

Table 4.5 (continued)

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]		Dose[c] (LED or HID), µg/mL	Reference
			Without exogenous metabolic system	With exogenous metabolic system		
2,2',4,4',5,5'-HexaCB	PCB-153	Micronucleus formation, human breast epithelial MCF-10A cells	+		0.4	Venkatesha et al. (2008)
2,2',4,4',5,5'-HexaCB	PCB-153	Micronucleus formation, human hepatoma HepG2 cells	+		36	Wei et al. (2009a)
2,2',4,4',5,5'-HexaCB	PCB-153	DNA strand breaks (comet assay), fish fibroblast RTG-2 cells	+		11	Marabini et al. (2011)
2,2',4,4',5,5'-HexaCB	PCB-153	Micronucleus formation, fish fibroblast RTG-2 cells	+		11	Marabini et al. (2011)
4-OH-2,2',3,4',5,5',6-HeptaCB	Metabolite of PCB-187	Detection of repairable adducts by growth inhibition (DRAG) assay in wildtype and DNA repair-deficient Chinese hamster ovary cells	–		23	Johansson et al. (2004)
2,2',3,3',4,4',5,5',6,6'-DecaCB	PCB-209	Gene mutation, mouse lymphoma L5178Y cells, *Tk*$^{+/-}$ locus	–	–	150	Han et al. (2009)

[a] BZ nomenclature as listed in Table 1.1, Section 1

[b] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative;?, considered to be inconclusive (variable responses in several experiments within an inadequate study); 0, not tested.

[c] Approximately minimal lethal dose not reported.

[d] Dose 140 µg/mL is the IC_{50} concentration inhibiting growth of wildtype CHO cells (AA8) by 50%; 102, 92 and 91 are the IC_{50} for repair-deficient CHO cells EM9, UV4 and UV5, respectively.

CB, chlorobiphenyl; HID, highest effective dose; HQ, hydroquinone; LED, lowest effective dose; MED, maximum effective dose; $MeSO_2$, methyl sulfonyl; OH, hydroxyl

For the nomenclature of PCB metabolites, the reader is referred to the review by Grimm *et al.* (2015).

Table 4.6 Genetic and related effects of PCB congeners and their metabolites in experimental animals in vivo

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]	Dose[c] (LED or HID)	Reference
4-MonoCB 4′-OH-4-MonoCB	PCB-3 Metabolite of PCB-3	Gene mutation, transgenic male BigBlue® rat, liver	+ –	113 ip × 4 82 ip × 4	Lehmann *et al.* (2007)
4-MonoCB 4′-OH-4-MonoCB	PCB-3 Metabolite of PCB-3	Gene mutation, transgenic male BigBlue® rat, lung	(+) (+)	113 ip × 4 (1/week) 82 ip × 4 (1/week)	Maddox *et al.* (2008)
4-MonoCB 4′-OH-4-MonoCB	PCB-3 Metabolite of PCB-3	Gene mutation, transgenic female BigBlue® rat, liver	– –	113 ip × 4 82 ip × 4	Jacobus *et al.* (2010)
2,2′,5,5′-TetraCB	PCB-52	Chromosomal aberrations (numerical and structural), female Sprague-Dawley rat, 70% hepatectomy, bone-marrow cells	–	10 ppm, 1 year	Meisner *et al.* (1992)
2,2′,5,5′-TetraCB	PCB-52	Chromosomal aberrations (numerical), female Sprague-Dawley rat, liver cells after 70% hepatectomy	– –	10 ppm × 7 mo 10 ppm × 12 mo	Sargent *et al.* (1992)
3,3′,4,4′-TetraCB	PCB-77	Chromosomal aberrations (numerical & structural), female Sprague-Dawley rat, 70% hepatectomy, bone-marrow cells	–	0.1 ppm, 1 year	Meisner *et al.* (1992)
3,3′,4,4′-TetraCB	PCB-77	Chromosomal aberrations (numerical), female Sprague-Dawley rat liver cells after 70% hepatectomy	 –	0.1 ppm × 7 mo 0.1 ppm × 12 mo	Sargent *et al.* (1992)
3,3′,4,4′-TetraCB	PCB-77	DNA strand breaks (comet assay) and micronucleus formation, fish (*Salmo trutta fario*) erythrocytes	–	0.9 µg/mL	Belpaeme *et al.* (1996b)
3,3′,4,4′-TetraCB and 2,2′,5,5′-tetraCB	PCB-77 + PCB-52	Chromosomal aberrations (numerical & structural), female Sprague-Dawley rat, 70% hepatectomy, bone marrow cells	+	0.1 + 10 for 1 year	Meisner *et al.* (1992)
3,3′,4,4′ -TetraCB + 2,2′,5,5′-tetraCB	PCB-77 + PCB-52	Chromosomal aberrations (numerical), female Sprague-Dawley rat liver cells after 70% hepatectomy	–	0.1 + 10 ppm for 7 mo	Sargent *et al.* (1992)
3,3′,4,4′,5-PentaCB	PCB-126	Gene mutation, transgenic Muta™Mouse fetus, day 18 of gestation, after exposure on day 10, in utero	–	0.5 po × 1	Inomata *et al.* (2009)
3,3′,4,4′,5-PentaCB	PCB-126	DNA adducts, M_1dG secondary oxidative DNA lesion, LC-MS/MS female Sprague-Dawley rat, liver	+	0.001 po × 5 per week for 53 weeks	Jeong *et al.* (2008)
2,2′,4,4′,5,5′-HexaCB	PCB-153	DNA adducts, M_1dG secondary oxidative DNA lesion, LC-MS/MS female Sprague-Dawley rat, liver	–	1 po × 5 per week for 53 weeks	Jeong *et al.* (2008)
2,2′,4,4′,5,5′-HexaCB	PCB-153	DNA adducts, M_1dG secondary oxidative DNA lesion, LC-MS/MS female Sprague-Dawley rat, brain	–	1 po × 5/week for 53 weeks	Jeong *et al.* (2008)

Table 4.6 (continued)

PCB congener Structural name	BZ nomenclature[a]	Test system	Results[b]	Dose[c] (LED or HID)	Reference
3,3′,4,4′,5-PentaCB and 2,2′,4,4′,5,5′-hexaCB	PCB-126 + PCB-153	DNA adducts, M_1dG secondary oxidative DNA lesion, LC-MS/MS female Sprague-Dawley rat, liver	+	0.0003 + 3 po × 5/ week for 53 weeks	Jeong *et al.* (2008)
3,3′,4,4′,5-pentaCB and 2,2′,4,4′,5,5′-hexaCB	PCB-126 + PCB-153	DNA adducts, M_1dG secondary oxidative DNA lesion, LC-MS/MS female Sprague-Dawley rat, brain	–	0.001 + 1 po × 5/week for 53 weeks	Jeong *et al.* (2008)
2,2′,3,3′,4,4′,5,5′,6,6′-DecaCB	PCB-209	Micronucleus formation, male and female Crl:CD1 mice bone-marrow cells	–	2000 po × 1	Han *et al.* (2009)
1 : 2 : 3 : 2 Mixture of 2,3′,4,4′,5-pentaCB, 2,2′,3,4,4′,5′-hexaCB, 2,2′,4,4′,5,5′-hexaCB, and 2,2′,3,4,4′,5,5′-heptaCB	PCB-118, PCB-138, PCB-153, PCB-180	DNA adducts, M_1dG secondary oxidative DNA lesion, LC-MS/MS female C57BL/6J mouse, liver	–	10 ng TEQ/kg bw ip × 1	Jeong *et al.* (2008)

[a] BZ nomenclature as listed in Table 1.1, Section 1.

[b] +, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an inadequate study)

[c] In-vivo tests, mg/kg bw

CB, chlorobiphenyl; HID, highest effective dose; ip, intraperitoneal; mo, month; LED, lowest effective dose; po, oral administration; TEQ, toxic equivalency; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; HPLC/ECD, high-performance liquid chromatography electrochemical detection; I-compounds, take from Table 4.3 or Table 4.4

7 months (Elo *et al.*, 1985). [The Working Group noted that the control group was not defined. The data on observed chromosomal aberration and sister chromatid exchange, and the statistical method used, were not provided.] The other study reported a non-significant increase by fourfold in the frequency of chromosomal aberration, but no increase in the frequency of sister-chromatid exchange in a group of 12 workers (Melino *et al.*, 1992).

In another report, the study group consisted of 45 randomly selected people (workers, residents, or children) living within 2 km of a capacitor-producing factory known to cause occupational and environmental exposure to PCBs, in Semic, Slovenia, and was compared to workers that had pre-employment tests. An abnormally high frequency of structural chromosome aberration (55%) was observed in peripheral lymphocytes from workers and residents when compared with the control group (Tretjak *et al.*, 1990). However, these findings were not correlated to environmental or blood PCB concentrations. [The Working Group noted that no PCB concentrations in blood were reported. No matched control group was available and no statistical analysis was performed. Heavy smokers and people who had had recent X-ray examinations were excluded from the study].

Men working in Chinese electrical and electronic equipment waste-dismantling factories were shown to be exposed occupationally to PCBs, tetrachlorodibenzo-*p*-dioxins and dibenzofurans (TCDD/Fs) and polybrominated diphenyl ethers (PBDEs). Urine concentrations of 8-hydroxydeoxyguanosine (8-OHdG), a product of oxidative DNA damage, were significantly increased in workers after their working shift when compared with levels before the working shift. However, no correlation could be drawn between the observed increase in urinary 8-OHdG concentrations and occupational exposure to any of the organochlorine compounds (Wen *et al.*, 2008).

(b) Genotoxicity and cytogenicity from non-occupational exposure

Three years after accidental contamination of cooking oil with PCBs in Taiwan, China (see Section 1.4.8), blood samples were taken from 36 patients with Yucheng ("oil disease"); lymphocytes were analysed for chromosomal aberrations and compared with lymphocytes from age- and sex-matched laboratory staff (n = 10). Blood PCB concentrations ranged from 6.4 to 101.8 μg/L. A high frequency of chromosomal aberration was observed in 19 out of 36 (53%) PCB-exposed patients, while none was seen in the control group. The findings could not be correlated with the blood PCB levels (Wuu & Wong, 1985). [The Working Group noted that no details on the statistical evaluation or adjustment for confounders were given.]

The frequencies of chromosomal aberration and sister-chromatid exchange in peripheral lymphocytes from 35 nonsmoking women from Taiwan, China, exposed to PCBs through contaminated rice oil ("Yucheng") were similar to those from matched controls. However, when peripheral blood lymphocytes were treated with α-naphthoflavone in vitro [to increase sensitivity], a small (20%) but significant increase in frequency of sister-chromatid exchange, but not chromosomal aberration, was observed (Lundgren *et al.*, 1987, 1988).

Similarly, 27 years after exposure to high concentrations of PCBs, the frequency of sister-chromatid exchange in lymphocytes of 16 victims of the "Yusho" food poisoning incident (see Section 1.4.8 in this *Monograph*) were not significantly different from those of a non-exposed control group, despite persistently elevated blood PCB concentrations in these patients (281 pg/g fat versus 41 pg/g fat in the control group). Addition of α-naphthoflavone did not increase the frequency of sister-chromatid exchange (Nagayama *et al.*, 2001).

Blood concentrations of cadmium, lead, *p,p′*-dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene, PCBs (PCB-99, PCB-118, PCB-170, PCB-138, PCB-153, PCB-180), and dioxin-like activity (Calux assay) were analysed in 1583 residents in nine different industrialized regions in Belgium (De Coster *et al.*, 2008). Also analysed as effect biomarkers were the percentage of cells with micronucleus formation, DNA damage (comet assay) in peripheral blood cells, and 8-OHdG in urine. Overall significant differences between the different regions were found for micronucleus formation, DNA damage, and urinary 8-OHdG concentrations. Among these, positive correlations were reported between PCB-118 concentrations and both micronucleus formation and DNA damage.

In a group of 103 Inuit people from Northern Canada exposed to high dietary concentrations of PCBs and selenium, plasma PCB concentrations and DNA adduct profiles in leukocytes were determined (Ravoori *et al.*, 2008). The ^{32}P-postlabelling technique used allowed for differentiation between polar and lipophilic adducts. Plasma PCB concentrations were significantly correlated with increasing age [$P < 0.01$]. The most abundant PCB congeners in the plasma were PCB-138, PCB-153, and PCB-180. The most abundant adduct was 8-OHdG, which accounted for 51–57% of the total adduct burden. No correlation between adduct levels and specific PCB congeners, smoking status, or sex were observed.

In a follow-up study in 83 subjects, Ravoori *et al.* (2010) reported 30–800-fold interindividual variability in levels of unidentified polar DNA adducts (indicative of oxidative stress) in leukocytes. Negative associations were observed between total DNA adduct levels and selenium, and PCB concentrations, the latter being significant. After grouping the individuals according to selenium/PCB ratio as high-ratio (ratio, > 33; mean, 75.5; $n = 41$), or low-ratio (ratio, ≤ 33; mean, 18; $n = 42$), levels of 8-OHdG and total DNA adducts were significantly negatively correlated with the high-ratio group ($P = 0.014$ and $P < 0.01$, respectively), while there was no correlation with the low-ratio group, indicating a mitigating effect of selenium on the toxicity of PCBs.

(c) *Sperm DNA damage*

Sex-chromosome disomy in sperm nuclei was determined in 192 men from subfertile couples. A positive association with YY, XY, and total sex-chromosome disomy and an inverse association with XX disomy were observed with higher serum concentrations of four PCBs (PCB-118, PCB-138, PCB-153, and PCB-180) (McAuliffe *et al.*, 2012). Other environmental organochlorine pollutants may also have contributed to sex-chromosome aneuploidy, since plasma DDE concentrations were positively associated with increased rates of XX, XY, and total sex-chromosome disomy.

In a group of 176 Swedish fishermen with low or high consumption of fatty fish, the DNA fragmentation index in sperm was compared with serum PCB concentrations (Rignell-Hydbom *et al.*, 2005). Plasma concentration of PCB-153 was statistically significantly associated with an increase in DNA fragmentation ($P < 0.001$); however, when adjusted for age, which was strongly associated with percentage DNA fragmentation index, this association was no longer significant ($P = 0.28$). When PCB-153 concentrations were categorized into quintiles, the lowest-exposure quintile had significantly lower levels of DNA fragmentation than the other quintiles ($P < 0.001$), even after adjustment for age ($P = 0.006$). The association between DNA fragmentation and DDE concentrations was not significant (Rignell-Hydbom *et al.*, 2005).

In sperm samples from 707 adult men (193 Inuits from Greenland, 178 Swedish fishermen, 141 men from Poland, and 195 men from Ukraine), DNA fragmentation was correlated with serum PCB-153 concentrations (Spanò *et al.*, 2005). After adjustment for age, period of sexual abstinence, and serum PCB-153 concentration,

levels of DNA fragmentation betwen men in the three European groups did not differ considerably, but were significantly higher than those found in Inuit men. While DNA fragmentation in sperm was unrelated to PCB-153 concentration among the Inuits (very high PCB concentrations) and Polish men (very low PCB concentrations), increasing serum PCB-153 concentrations were significantly associated with increased DNA fragmentation in the Swedish (P = 0.001), and Ukranian cohorts (P = 0.027), and in the three European groups combined (P < 0.0001). No correlation between DNA fragmentation index and serum DDE concentrations was seen.

Similar results were observed in a subsequent study with a largely overlapping study population (Stronati *et al.*, 2006).

(d) Gene mutation

A possible correlation between PCB exposure and cancer of the pancreas has been discussed earlier (see Section 2.3.5). An analysis of blood organochlorine concentrations and *KRAS* mutations in tissue from pancreatic cancer found a significant correlation between tumours harbouring *KRAS* mutations and PCB-138, and PCB-153, and between the two most common mutations in *KRAS* and PCB-138 concentrations (Porta *et al.*, 2009). The dose–response pattern was approximately linear only for PCB-138.

Another study analysed post-mortem samples of brain from patients with neurodevelopmental disorders with a known genetic basis (n = 32), autism of unknown etiology (n = 32), and controls (n = 43) for eight PCBs (PCB-28, PCB-95, PCB-105, PCB-118, PCB-138, PCB-153, PCB-170, and PCB-180) (Mitchell *et al.*, 2012). The concentration of PCB-95 was significantly higher in the group with genetic neurodevelopmental diseases. In fact, PCB-95 was detected nearly exclusively in the brain of patients from mothers with a specific duplication in the long arm of chromosome 15 (dup15q11–q13) or deletions in the same chromosome 15q11–q13 in patients with Prader-Willie syndrome. Five out of six patients with dup15q11–q13, which is related to autism spectrum disorder, were born after 1976.

(e) Epigenetic effects

In the study by Mitchell *et al.* (2012) cited above, samples of brain showing dup15q also showed a lower level of methylation in regions of repetitive DNA, suggesting that PCBs may have caused hypomethylation in these regions, resulting in chromosome instability and a higher risk of duplication.

Rusiecki and coworkers used pyrosequencing to estimate global DNA methylation via repetitive elements *Alu* and (long interspersed nucleotide element) LINE-1 assays of bisulfite-treated DNA in 70 samples from Inuit people in Greenland to examine epigenetic effects of high PCB contamination (Rusiecki *et al.*, 2008). They observed significant inverse correlations between percentages of methylcytosine and plasma concentrations of DDT, DDE, β-hexachlorocyclohexane, oxychlordane, α-chlordane, mirex, sum of PCBs, and sum of all persistent organic pollutants, after adjusting for age and cigarette smoking.

(f) Changes in gene expression

In samples taken in 2007 from 139 daughters of members of a cohort of fish-consumers in Michigan, there was no correlation between serum concentrations of PCB, PBDE, or DDE, and expression of four genes encoding 17-α-hydroxylase (CYP17A1), aromatase (CYP19A1), and estrogen receptor α and β (ESR1 and ESR2) (Karmaus *et al.*, 2011). In contrast, maternal concentrations of serum PCB (prenatal PCB concentration), measured in 1973–1991, were highly significantly associated with decreased expression of the steroid synthesis genes *CYP17* and *CYP19* in blood lymphocytes. Other persistent organic pollutants were not correlated.

4.2.2 Experimental systems

(a) Commercial PCB mixtures

Table 4.3 and Table 4.4 summarize data with commercial PCB mixtures in in-vitro and in-vivo studies respectively. For each category of test (non-mammalian systems, mammalian cells in vitro, and in-vivo assays), the data are presented by commercial PCB mixture in increasing order of chlorination, and for each commercial mixture, by end-point.

(i) Non-mammalian systems

All PCB mixtures tested for their ability to induce gene mutation in bacteria, i.e. PCB mixtures with chlorination levels ranging from ~20% (e.g. Aroclor 1221) to ~70% (e.g. Aroclor 1268) were not mutagenic in different strains of *Salmonella typhimurium* and *Escherichia coli* in the absence or presence of an exogenous metabolic activation system comprising induced and non-induced liver microsomes (Table 4.3). However, only Aroclor 1254 was tested up to the recommended limit dose for hazard assessment of 5000 µg/plate (Shahin *et al.*, 1979), not all strains typically used in the Ames test battery (*S. typhimurium* TA98, TA100, TA1535, TA1537) or *E. coli* WP2 *uvrA* were tested, and an exogenous metabolic system was not always included.

In contrast, Aroclor 1221 and Aroclor 1260 did induce intrachromosomal recombination in *Saccharomyces cerevisiae* cells in the absence and presence of exogenous metabolic activation. Since Aroclor 1221 was effective at lower concentrations than Aroclor 1260, chlorination level seemed to be inversely correlated to mutagenicity of PCBs in this test system (Schiestl *et al.*, 1997).

Additionally, Aroclor 1254 induced mutations in the number of tandem repeats in *S. cerevisiae* transgenic for the human MS32 minisatellite (Appelgren *et al.*, 1999).

Clophen mixtures did not induce somatic mutation in the fruit fly *Drosophila melanogaster* (Nilsson & Ramel, 1974).

(ii) Mammalian cells in vitro

Aroclor 1254 caused DNA strand breaks (detected by alkaline filter elution) in primary rat hepatocytes (Sina *et al.*, 1983) and in primary rat prostate cells (comet assay; Cillo *et al.*, 2007), while evidence for induction of unscheduled DNA synthesis in primary rat hepatocytes was equivocal (Probst *et al.*, 1981; Althaus *et al.*, 1982). An increase in the frequency of DNA adducts (detected by ^{32}P-postlabelling) was observed in primary human hepatocytes from three different donors (Borlak *et al.*, 2003), but not in cultured human hepatocarcinoma HepG2 cells or dexamethasone-treated primary rat fetal hepatocytes (Dubois *et al.*, 1995). A dose-dependent increase in structural chromosomal aberration starting at concentrations of less than 1 µg/mL was seen in cultured human lymphocytes (Sargent *et al.*, 1989).

Aroclor 1221 caused intrachromosomal recombination at the *Hprt* locus in a mutant Chinese hamster V79 cell line (Helleday *et al.*, 1998), and in human lymphoblastoid cells (Aubrecht *et al.*, 1995). Aroclor 1016 enhanced DNA-adduct formation in primary human lymphocytes (Borlak *et al.*, 2003); no increase in the frequency of chromosomal aberration was seen in chicken embryos and ouabain-resistant colonies in Chinese hamster V79 cells treated with Aroclor 1242 (Blazak & Marcum, 1975; Hattula, 1985).

(iii) In-vivo assays

Repeated doses of Aroclor 1254 did not alter hepatic levels of DNA adducts (as measured by ^{32}P-postlabelling) in male Sprague-Dawley (given two intraperitoneal doses of 500 mg/kg bw) or male Fischer 344 rats (given 35 oral doses of 25 mg/kg bw) compared with controls (Nath *et al.*, 1991; Chadwick *et al.*, 1993).

When used for hepatic enzyme induction, a single intraperitoneal application of Aroclor 1254 of up to 500 mg/kg bw in rats (Kornbrust & Dietz, 1985; Shaddock *et al.*, 1989) and 50 mg/kg bw

in cynomolgus monkeys (Hamilton *et al.*, 1997) did not enhance unscheduled DNA synthesis in isolated primary hepatocytes.

Dietary exposure of male C57BL/6 (Big Blue®) mice transgenic for bacterial *lacI* to Aroclor 1254 at 100 ppm (0.01%) for 7 weeks caused a significant, but less than twofold, increase in the frequency of mutation in the liver (Davies *et al.*, 2000).

No increase in the frequency of structural chromosomal aberration in bone marrow and spermatogonial cells was observed in rats given repeated doses of Aroclor 1254 by gavage (300 mg/kg bw for five consecutive days or 50 mg/kg bw for seven consecutive days) or in the diet (500 ppm for 5 weeks) (Dikshith *et al.*, 1975; Green *et al.*, 1975a; Garthoff *et al.*, 1977). Aroclor 1254 did not increase the frequency of micronucleus formation in bone marrow of $B6C3F_1$ mice given Aroclor 1254 as intraperitoneal injections of 15 000 mg/kg bw on five consecutive days (Bruce & Heddle, 1979).

In contrast to the observations in rodents, a single intraperitoneal injection of Aroclor 1254 induced a dose-dependent increase in the frequency of micronucleus formation in fish (*Cyprinus carpio*) erythrocytes (Al-Sabti, 1986), and aberrant metaphases and structural chromosomal aberration in fish kidney cells (*Cyprinus carpio*, *Tinca tinica*, *Ctenopharyngodon idella*), from the starting dose of 50 mg/kg bw (Al-Sabti, 1985). In addition, Aroclor 1254 induced germline length mutation in the PC-1 but not PC-2 minisatellite region in male C57B1/6 mice given a single intraperitoneal dose of Aroclor 1254 at 100 mg/kg bw (Hedenskog *et al.*, 1997).

Kanechlor 500 (which has a similar level of chlorination as Arochlor 1254) caused a weak (less than twofold) increase in the frequency of micronucleus formation in bone-marrow cells in male ddY mice given an oral dose at 100 mg/kg bw for 6 days, but not when applied subcutaneously at the same dose (Watanabe *et al.*, 1982).

A single dose of Aroclor 1242 did not enhance levels of DNA adducts (as measured by ^{32}P-postlabelling) or 8-OHdG formation (as measured by high-performance liquid chromatography/electrochemical detection) in liver, glandular stomach, spleen, thymus, prostate, testes, and seminal vesicles of male Lewis rats, nor did Aroclor 1242 induce structural chromosomal aberrations in bone marrow and spermatogonial cells of Osborne-Mendel rats given a single oral dose of 5000 mg/kg bw, or repeated doses of 500 mg/kg bw for 4 days (Green *et al.*, 1975a; Schilderman *et al.*, 2000).

Aroclor 1242, like Aroclor 1254, did not reduce the number of mitotic spermatogonial cells in Osborne-Mendel rats at the highest doses tested (Green *et al.*, 1975a), and had no effect on the number of dominant lethals (Green *et al.*, 1975b).

A study by Desaulniers *et al.* (2009) examined the effects of PCB and organochlorine pesticide mixtures on DNA methylation in the liver of exposed rats. The PCB mixture, but not the organochlorine pesticide mixture, reduced the mRNA abundance of DNA methyltransferase-1, -3a, and -3b, reduced the abundance of the methyl donor *S*-adenosylmethionine, and decreased the methylation of CpG sites in the promoter region of the tumour suppressor gene $p16^{INK4a}$.

Another group analysed histone post-translational modifications in chromatids from liver of rats exposed to PCBs in early life (Casati *et al.*, 2012). There was a decrease in levels of histone H4K16Ac and histone H3K4me3, and an increase in the expression of *SirtT1* and *Jarid1b*, genes encoding two chromatid-modifying enzymes (histone demethylases). A decrease in the abundance of mRNA of androgen receptor, a histone enzyme coregulator, was also reported.

Ghosh *et al.* (2011) applied the tools of global gene expression and Ingenuity biological functions analysis to peripheral blood mononuclear cells (PBMC) exposed in vitro to PCB-138 (0.87 ng/mL) or PCB-153 (1.42 ng/mL) for 48

hours. The expression of several biologically significant genes was highly modulated in vitro, in general by downregulation, and differential gene expression was specific to the PCB used. Exposure to PCB-153 identified genes involved in three Ingenuity Pathway Analysis (IPA) networks involved in cellular movement, development and function of the haematological system, immune cell trafficking, molecular transport, and cancer. Exposure to PCB-138 resulted in significant expression of several genes including tumour necrosis factor-associated protein 1 (*TRAP1*), contactin 5 (human neuronal NB-2 gene) (*CNTN5*), glial cell line-derived neurotrophic factor family receptor α-1 (*GFRA1*), von Willebrand factor D and EGF domains (*VWDE*), and *CYP1A2*. Notable among these are the upregulated genes *TRAP1*, *CNTN5*, *GFRA1*, which are important in the activation of *TRAP-1*.

Using the same genomic methods, Hochstenbach *et al.* (2010) reported alterations indicative of exposure to immunotoxicants in whole genome gene-expression profiles (transcriptomic changes) in human PBMC from two healthy donors exposed in vitro to a range of immunotoxic chemicals including PCB-153.

Wens *et al.* (2013) studied gene-expression profiles in PBMC exposed in vitro to a dioxin-like polychlorinated biphenyl, PCB-126 (1 μM), or a non dioxin-like polychlorinated biphenyl, PCB-153 (10 μM). Hierarchal cluster analysis created distinct clustered gene groups for samples exposed to PCB-126 or PCB-153. The number of differentially expressed genes varied with the compound used and ranged from 60 to 192. As expected, exposure to PCB-126 caused induction of the AhR signalling pathway. Exposure to PCB-153, which is known to disrupt thyroid metabolism, resulted in expression of the nuclear estrogen receptor *ESR2*.

(b) Individual congeners and their metabolites

In this section, the data in the text are presented first for non-mammalian systems and then combined for cell culture tests and in-vivo assays, by PCB congener and corresponding metabolite(s) (Table 4.5 and Table 4.6). Data in the table are presented first for non-mammalian systems and cell culture tests (Table 4.5), and then for in-vitro assays (Table 4.6).

(i) Non-mammalian systems

In tests for gene mutation in bacteria, the PCB congeners PCB-1, PCB-3, PCB-15, PCB-47, PCB-52, PCB-77, PCB-155, and PCB-209 were not mutagenic in various strains of *Salmonella typhimurium* and *Escherichia coli* in the absence or presence of exogenous metabolic activation (induced and non-induced liver microsomes), except in one study with PCB-3 in *S. typhimurium* TA1538 in the presence of rabbit liver microsomes (Wyndham *et al.*, 1976). Only PCB-209 was tested up to the recommended limit dose of 5000 μg/plate and in all strains typically used in the Ames test battery, i.e. *S. typhimurium* TA98, TA100, TA1535, TA1537, and in *E. coli* WP2 *uvrA* (Han *et al.*, 2009).

The less chlorinated congener PCB-15 was reported to induce somatic mutation in *Drosophila melanogaster* (Butterworth *et al.*, 1995).

(ii) Cell culture tests and in-vivo assays

Several studies have shown in vitro or in non-humans in vivo that PCB congeners with one to four chlorine atoms are bioactivated to DNA- and protein-binding intermediates in vitro and in vivo. Each congener produced multiple different DNA adducts, particularly with guanine. The most prominent ultimate DNA-binding intermediates were quinone metabolites, but some binding of epoxide intermediates was suggested. Rodent and human liver microsomes produced similar or different adduct patterns depending on the PCB congener used, indicating that

species differences exist. Reactive intermediates can bind to cellular macromolecules, including DNA and DNA-maintenance proteins, and such adducts can be detected in multiple organs (Morales & Matthews, 1979; Amaro *et al.*, 1996; McLean *et al.*, 1996b; Oakley *et al.*, 1996a, 1996b; Lin *et al.*, 2000; Pereg *et al.*, 2001, 2002; Srinivasan *et al.*, 2002; Arif *et al.*, 2003; Zhao *et al.*, 2004; Bender *et al.*, 2006; Bender & Osheroff, 2007).

PCB-1, PCB-2, PCB-3 and metabolites

Without exogenous metabolic activation, tritium-labelled PCB-3 was reported to bind to DNA, RNA, and cellular proteins in cultured Chinese hamster ovary cells (Wong *et al.*, 1979). PCB-3 also enhanced unscheduled DNA synthesis by 1.6-fold in the same cell line (Wong *et al.*, 1979), and increased DNA-adduct formation dose-dependently in primary human hepatocytes, as determined by ^{32}P-postlabelling (Borlak *et al.*, 2003). Maximum adduct levels were observed 24 hours after exposure and declined to control levels within 48 hours (Borlak *et al.*, 2003).

The mutagenicity of PCB-3, its mono- and dihydroxylated metabolites, and its 3′,4′- and 2′,5′-quinones was investigated in cultured Chinese hamster V79 cells (Zettner *et al.*, 2007). Induction of gene mutations at the *Hprt* locus was determined by 6-thioguanine resistance. Induction of chromosomal and genomic mutation was assessed by micronucleus formation and immunochemical differentiation of micronuclei containing whole chromosomes (kinetochore-positive) or DNA fragments (kinetochore-negative). Both quinones, but not the PCB-3 itself or its mono- or dihydroxylated metabolites, caused a dose-dependent increase in the frequency of 6-thioguanine-resistant colonies at non-cytotoxic concentrations, and an increase in chromosomal and genomic mutation was observed at higher, cytotoxic concentrations.

In addition, the 2′,5′-dihydroxylated metabolites of PCB-3 and PCB-2, but not of PCB-1, or the 3′,4′-dihydroxy-PCB-3 induced polyploidy in V79 cells; of these dihydroxylated metabolites, only 3′,4′-dihydroxy-PCB-3 increased the levels of sister-chromatid exchange (Flor & Ludewig, 2010).

As in V79 cells, PCB-3–2′,5′-quinone caused a dose-dependent increase in the frequency of micronucleus formation in human breast epithelial MCF-10A cells (Venkatesha *et al.*, 2008). At the concentrations tested, electron paramagnetic resonance showed an increase in steady-state levels of ROS, and detected the presence of a semiquinone radical, suggesting redox cycling of the 2′,5′-quinone. Furthermore, the increase in number of micronucleated cells observed with PCB-3–2′,5′-quinone and also with PCB-153 was consistent with an increase in levels of phosphorylated histone protein γ-H2AX (Venkatesha *et al.*, 2008). The 2′,5′-quinone of PCB-3 also caused significant and dose-dependent shortening of the telomeres in human keratinocyte HaCaT cells after 11 weeks of exposure, and an increase in frequency of micronucleus formation in V79 cells (Jacobus *et al.*, 2008).

Induction of gene mutation in vivo by PCB-3 and its monohydroxylated metabolite 4′-OH-PCB-3 was investigated in male and female transgenic Fischer 344 (Big Blue®) rats given four intraperitoneal injections of PCB-3 at 113 mg/kg bw and 4′-OH-PCB-3 at 82 mg/kg bw over 4 weeks. Seventeen days after the last injection, the frequency and spectrum of mutation in the *lacI* gene were determined in the liver (Lehmann *et al.*, 2007) and lung (Maddox *et al.*, 2008) of males, and in the liver of females (Jacobus *et al.*, 2010). Both PCB-3 and its 4′-OH-metabolite caused a similar, more than twofold, increase in mutation frequency in the liver of male rats; however, only the increase observed with PCB-3 was statistically significant. Although the mutation spectrum induced by PCB-3 was different from that in control rats, and similar to that induced by the positive control, 3-methylcholanthrene, only the proportion of transitions was statistically different from that in control

rats. In contrast, the mutation spectrum for 4′-OH-PCB-3 differed only slightly from that in the control group (Lehmann *et al.*, 2007). In the liver of female rats treated with PCB-3 and its 4′-OH-metabolite, mutation frequencies and mutation spectra were not significantly different from those observed in control rats (Jacobus *et al.*, 2010). PCB-3 and its 4′-OH-metabolite caused a twofold, but not statistically significant, increase in mutation frequency in the lungs of treated males. However, a shift in the mutation spectra, especially with PCB-3, and an increase in the frequency of mutation outside of the hotspot region for spontaneous mutation of *lacI* (base pairs 1–400) were observed (Maddox *et al.*, 2008). The genotoxicity profile of metabolites of PCB-3 is summarized in Table 4.7.

PCB-28, PCB-52, PCB-77

PCB-52 enhanced the frequency of DNA strand breaks in human lymphocytes (comet assay) and mouse fibroblast L-929 cells (alkaline sedimentation), but had no effect on the level of sister-chromatid exchange and structural chromosomal aberration in human lymphocytes (Stadnicki & Allen, 1979; Stadnicki *et al.*, 1979; Sargent *et al.*, 1989; Sandal *et al.*, 2008). However, the addition of PCB-77 at non-genotoxic concentrations led to a threefold increase in the frequency of chromatid breaks compared with that in control cells (Sargent *et al.*, 1989).

PCB-28, PCB-52, and a synthetic mixture of PCBs similar to that present in air in Chicago, USA, at equimolar concentrations all caused a 30–40% reduction in telomerase activity in human skin HaCaT keratinocytes, but the effect on telomere length differed, with shortening effects caused by PCB-28, PCB-52, and the Chicago air mixture of about 10%, 40%, and 5%, respectively, compared with controls after 6 weeks of exposure (Senthilkumar *et al.*, 2011).

PCB-77 caused DNA-adduct formation in human hepatocarcinoma HepG2 cells and in dexamethasone-treated primary rat fetal hepatocytes. In human lymphocytes, PCB-77 induced structural chromosomal aberration, but no increase in the frequency of micronucleated cells and sister-chromatid exchange was observed (Sargent *et al.*, 1989; Dubois *et al.*, 1995; Belpaeme *et al.*, 1996b).

Long-term dietary exposure of female hepatectomized Sprague-Dawley rats to PCB-52 at 10 ppm for 7 months, or PCB-77 at 0.1 ppm for 1 year, did not enhance the frequency of structural or numerical chromosomal aberration in liver and bone-marrow cells (Meisner *et al.*, 1992). However, coexposure to PCB-52 and PCB-77 at the doses given above for 1 year increased the frequency of polyploidy and structural chromosome aberration in bone-marrow cells. Although the frequency of numerical and structural chromosomal aberration in primary hepatocytes remained unaffected after coexposure to PCB-52 and PCB-77 for 7 months, the liver became more susceptible to diethylnitrosamine-induced genotoxicity (Sargent *et al.*, 1992).

PCB-101, PCB-118, PCB-138

PCB-101, PCB-118, and PCB-138 were able to induce DNA strand breaks (comet assay) and micronucleus formation (except PCB-138) in fish fibroblast RTG-2 cells [usually not used for genotoxicity testing], in a single dose experiment. However, the time course of markers for oxidative stress (carboxy-dichlorofluorescein oxidation, intracellular GSH, lipid peroxidation, and superoxide dismutase activity) did not correspond with the observed genotoxicity (Marabini *et al.*, 2011).

PCB-126

PCB-126 did not increase the frequency of micronucleus formation in human hepatoma HepG2 cells, but did cause a significant, but not dose-dependent, increase in levels of the DNA repair protein XPA (Western blot), whereas XPC protein levels were unaffected (Wei *et al.*, 2009b).

Table 4.7 Genotoxicity profile of metabolites of PCB-3

Compound	Lowest effective dose (μM)						
	Gene mutation (thioguanine resistance)[a]	Micronucleus (clastogenic effect)[a]	Micronucleus (aneuploidy: chromosomal loss)[a]	SCE[b]	Polyploidy[b]	DNA damage (comet assay)[c]	ROS[c]
PCB-3	-	-	-	-	-	-	-
2-OH-PCB-3	-	-	50	-	-	-	-
3-OH-PCB-3	-	-	100	-	-	-	-
4-OH-PCB-3	-	75	75	-	-	-	-
3,4-dihydroxy-PCB-3	-	25	15	5	-	-	-
3,4-*ortho*-quinone	0.6	15	5	-	-	-	-
2,5-hydroquinone	-	5	2.5	-	7.5	10 (at 37°C, not 6°C, in HL-60 cells; not in Jurkat cells at 37°C)	5 (ROS increased in HL-60 cells at 37°C, not at 6°C; no effect on ROS in Jurkat cells)
2,5-*para*-quinone	0.5	1	2.5	-	-	5 (at 37°C or 6°C in HL-60 cells; at 37°C in Jurkat cells)	2.5 (ROS increased in HL-60 cells and in Jurkat cells)

[a] From Zettner *et al.* (2007)
[b] From Flor & Ludewig (2010)
[c] From Xie *et al.* (2010)
PCB, polychlorinated biphenyl; ROS, reactive oxygen species; SCE, sister-chromatid exchange
Adapted from Robertson & Ludewig (2011)

PCB-126 did not increase the frequency of mutation in fetuses of the transgenic Muta™Mouse on day 18 of gestation after a single maternal oral dose of 0.5 mg/kg bw on day 10 of gestation (Inomata *et al.*, 2009).

PCB-126 and PCB-153

The role of oxidative DNA damage in carcinogenesis caused by PCB-126, PCB-153, and a combination thereof, was investigated by measuring in treated animals the accumulation of a DNA adduct, namely 3-(2′-deoxy-β-D-erythro-pentafuranosyl)-pyrimido[1,2-α]-purin-10-one (M1dG) (the pyrimidopurinone of deoxyguanosine) (Dedon *et al.*, 1998), which can be formed by reaction of lipid-peroxidation derived malonedialdehyde or by oxidation of deoxyribose-derived DNA base propenal and deoxyguanosine. Accumulation of M1dG adducts was assessed in the liver of female C57BL/6J mice given a single dose and in Sprague-Dawley rats exposed for 1 year. A single dose of a mixture consisting of four dioxin-like compounds (including PCB-126), or a mixture consisting of four non-dioxin-like PCBs (PCB 118, 138, 153, 180), did not increase M1dG accumulation in the mouse liver. In female Sprague-Dawley rats exposed to PCB-126, PCB-153, or a combination of both for 1 year (see Section 3; NTP, 2006a, b, c), an increase in hepatic levels of M1dG was observed in rats treated with PCB-126, and in rats treated with a combination of PCB-126 + PCB-153. In female rats coexposed to PCB-126 + PCB-153, the observed levels of M1dG adducts correlated with the observed incidence of liver tumours (Jeong *et al.*, 2008).

PCB-153

PCB-153 induced structural chromosomal aberration in human lymphocytes (Sargent *et al.*, 1989) and a statistically significant dose-dependent increase in the frequency of micronucleus formation in human breast epithelial MCF-10A cells (Venkatesha *et al.*, 2008). PCB-153 also induced a significant and dose-dependent twofold increase in the frequency of micronucleation in human hepatocarcinoma HepG2 cells. Coexposure to PCB-153 and benzo[*a*]pyrene significantly and dose-dependently increased the frequency of micronucleus formation by 60%. When α-naphthoflavone (an inhibitor of CYP1A1) was added to cultures exposed to PCB-153 and PCB-153 + benzo[*a*]pyrene, the frequency of micronucleation decreased almost to control levels (Wei *et al.*, 2009a).

PCB-153 was able to induce DNA strand breaks and micronucleus formation in fish fibroblast RTG-2 cells (Marabini *et al.*, 2011; see above for comments).

Treatment of immortal human skin HaCaT keratinocytes with PCB-153 at a single concentration resulted in a decrease in telomerase activity (~20% after 1 week to ~40% after 7 weeks of exposure) and telomeres were shortened by about 40% (Senthilkumar *et al.*, 2012). Shortening of telomeres was also observed in normal human foreskin keratinocytes exposed to PCB-153 in culture, but the difference compared with the control cells was not statistically significant on any of the days analysed.

PCB-209

PCB-209 did not induce mutation at the thymidine kinase locus in mouse lymphoma L5178Y/$T^{+/-}$ cells, and did not cause an increase in micronucleus formation in bone-marrow cells of male and female Crl:CD1 mice given a single oral dose at 2000 mg/kg bw (Han *et al.*, 2009).

$MeSO_2$-PCB metabolites

$MeSO_2$-PCBs did not induce micronucleus formation in cultured human lymphocytes, but some, namely 3-$MeSO_2$-2,5,2′,4′,5′-pentaCB [3′-$MeSO_2$-PCB-101;3-$MeSO_2$-2,2′,4′,5,5′-pentaCB] and 4-$MeSO_2$-2,5,2′,3′,4′-pentaCB [4’-$MeSO_2$-PCB-87; 4-$MeSO_2$-2,2′,3′,4′,5- pentaCB], enhanced levels of sister-chromatid exchange (Nagayama *et al.*, 1995, 1999).

(c) Summary

Numerous cell-based test systems, and animal models, have been used to investigate the genotoxic potential of commercial PCB mixtures. However, only 13 individual congeners have been examined so far in studies of genotoxicity and related effects. Seven congeners (PCB-3, PCB-52, PCB-77, PCB-118, PCB-138, PCB-153, PCB-209) have been investigated in both cellular systems and animals. An additional four congeners (PCB-15, PCB-47, PCB-101, and PCB-155) were tested only in cellular systems, and two congeners (PCB-126 and PCB-180) have been tested only in cellular systems or animals, respectively.

Studies on induction of gene mutation in bacteria exposed to PCB mixtures, or to the few individual congeners tested, gave negative results. However, these data were of limited value for assessing this end-point because the doses applied were usually < 1000 µg/plate and/or where this was not the case, testing with an exogenous metabolic system was omitted. Studies with PCB-209 were not subject to the aforementioned limitations.

When high concentrations of commercial PCB mixtures were tested in *Saccharomyces cerevisiae*, genotoxicity was observed with Arochlor 1254, Aroclor 1221, and Aroclor 1260. In mammalian cells in vitro, Aroclor 1254 was reported to produce DNA adducts, unscheduled DNA synthesis, DNA strand breaks and, to some extent, chromosomal aberration. Although these end-points were negative when tested in rodents in vivo, Aroclor 1254 did increase chromosomal aberration and micronucleation in fish, and mutation frequency in the liver of transgenic Big Blue® mice. Aroclor 1254 induced cell transformation in cultured Syrian hamster embryo cells.

As for the individual congeners, the most comprehensive data on genetic effects were available for PCB-3 and its metabolites. PCB-3 did not induce gene mutation in bacteria at doses up to 1000 µg/plate in the presence or absence of an exogenous metabolic system, except for one study in strain TA1538 in the presence of rabbit liver microsomes (see Table 4.4). However, PCB-3 was reported to bind to DNA and to cause an increase in levels of DNA adducts in primary human hepatocytes.

The cell lines commonly used for mutagenicity testing (Chinese hamster lung fibroblast V79, Chinese hamster ovary fibroblast, and mouse lymphoma L5178Y cells) have no or only very limited biotransformation capability, a problem for test compounds that require metabolic activation. Using instead a series of synthetic PCB-3 metabolites in the V79 gene mutation assay, the *ortho* (3,4-) and *para* (2,5-) quinones were shown to efficiently induce mutation at the *Hprt* locus at non-cytotoxic concentrations, while none of the tested mono- or dihydroxylated metabolites or PCB-3 itself induced mutation (see Table 4.4). In addition, an increase in chromosomal and genomic mutation was observed for all tested PCB-3 metabolites at higher, cytotoxic concentrations. Also, the 2′,5′-dihydroxylated metabolites of PCB-3 and PCB-2, but not metabolites of PCB-1 or the 3′,4′-dihydroxylated PCB-3, induced polyploidy in V79 cells, indicating strict structure–activity requirements for this type of DNA damage. The 2′,5′-quinone of PCB-3 induced an increase in levels of ROS via a semiquinone radical at concentrations inducing micronucleation, suggesting redox cycling of the 2′,5′-quinone. PCB-3–2′,5′-quinone caused telomere shortening in cultured HaCaT cells exposed for 11 weeks, an effect that may have been caused by oxidative stress.

The mutagenic activity of PCB-3 was also tested in an assay in transgenic rats in vivo. In the liver of male rats exposed to PCB-3, the mutation frequency was significantly increased and the mutation spectrum changed from predominantly transitions in the controls to predominantly G:C → T:A transversions in the rats exposed to PCB-3. 4′-OH-PCB-3 caused a similar, but not statistically significant, increase

in mutation frequency and a minor shift in the mutation spectrum compared with rats in the control group. A sex-specific and organ-specific difference was noted, since the response was less pronounced in livers of female Big Blue® rats and lungs of males, in which the observed increases in mutation frequency were below the level of statistical significance.

The non-dioxin-like PCB-52 was not tested for gene mutation in bacteria and cultured mammalian cells. Data on chromosomal aberration in cultured mammalian cells were ambiguous, but also of limited value since PCB-52 was never tested in the presence of a metabolic activation system. There were, however, indications of DNA damage caused by PCB-52 metabolites in studies in vitro and in vivo in rats coexposed to PCB-52 and dioxin-like PCB-77 for 1 year. Negative outcomes in other studies of chromosomal aberration in vivo may be attributed to the low doses tested.

The dioxin-like PCB-77 increased the level of DNA adducts in cultured mammalian cells. The lack of data on mutagenicity testing of PCB-77 did not allow for an interpretation of these findings with regard to gene mutation. Data on structural/numerical chromosomal aberrations, including micronucleus formation, were inconclusive in vitro, and negative for chromosomal aberration in female rats after long-term dietary exposure.

The limited data available on PCB-126 suggested no genotoxic potential in vitro or in vivo. However, increased levels of DNA adduct (M_1dG) indicative of the formation of ROS and/or lipid peroxidation were seen in female rats exposed to PCB-126 and PCB-126 + PCB-153 for 1 year (Jeong *et al.*, 2008).

Non-dioxin like PCB-153 gave positive results when tested for micronucleus formation in two cultured mammalian cell lines and one fish cell line. Also, reduction in telomerase activity corresponding to shortened telomeres was reported in cultured human cells. [Since no in-vivo data were available, the significance of these in-vitro results could not be assessed by the Working Group.]

For the decachlorinated PCB-209, a series of standard assays for genotoxicity that followed internationally accepted testing guidelines for regulatory purposes were performed under good laboratory practice (GLP) conditions, and showed no mutagenic and/or genotoxic potential.

4.3 Biochemical and cellular effects

4.3.1 AhR binding and activation

(a) AhR activity

AhR is a cytosolic, ligand-activated transcription factor that mediates many toxic and carcinogenic effects in vertebrates. TCDD has extremely high affinity to the AhR and is the reference AhR agonist and toxicant. AhR-mediated toxic responses are consequences of deregulated physiological functions, and sustained (chronic) AhR activation by persistent "dioxin-like" compounds is the key process in dioxin-like toxicity (Bock & Köhle, 2006). Toxicological evaluation of dioxin-like-PCBs (DL-PCBs) is based on various end-points associated with activation of the AhR and AhR-mediated physiological and toxic responses (Haws *et al.*, 2006). The major advantages of this concept are that most (if not all) effects of dioxin-like compounds are mediated via AhR activation, and that various effects of TCDD reported in many in-vivo and in-vitro models associated with carcinogenesis and tumour promotion may be extrapolated for DL-PCBs (IARC, 2012).

Effects of AhR-mediated changes in gene expression include the control of xenobiotic-metabolizing enzymes, modulations in cell cycle progression and cell proliferation, suppression of apoptosis, and perturbation of various developmental signalling pathways involved in carcinogenic processes (Vezina *et al.*, 2004; Sartor *et al.*, 2009; Faust *et al.*, 2013). In addition, AhR interacts with other signalling and transcription pathways,

including estrogen, thyroid and retinoic acid receptors, mitogen-activated protein kinases (MAPKs), NF-κB, retinoblastoma protein, and hypoxia-inducible factor-1 α (Tian *et al.*, 2002; Beischlag *et al.*, 2004; Murphy *et al.*, 2007; Puga *et al.*, 2009). Several molecular mechanisms that are related to AhR and that may contribute to carcinogenesis have been proposed:

- Induction of CYP1 enzymes linked to toxicity and cancer initiation (DNA-adduct formation and oxidative DNA damage);
- Sustained AhR-dependent expression of genes directly or indirectly controlling the cell cycle, proliferation and apoptosis, and cross-talk between genes in the AhR and growth-regulatory pathways;
- AhR-mediated cytoskeletal remodelling, reduced cell–cell contacts, modulation of developmental/differentiation pathways, cell plasticity and invasiveness affecting tumour progression;
- Upregulation of proinflammatory genes (Gasiewicz *et al.*, 2008).

Correlations between the immunosuppressive effects of PCBs and activation of the AhR pathway have been also reported (see Section 4.3.4).

(b) Concepts of TEF and TEQ

The concept of toxic equivalency (TEQ) is based on a common mechanism of action (mediated through AhR activation) of persistent organic pollutants (including polyhalogenated dibenzo-*p*-dioxins, dibenzofurans and biphenyls). It uses relative effective potencies (REP) of individual compounds to activate the AhR, and AhR-dependent toxic or biological effects relative to the reference toxicant TCDD; toxic equivalency factors (TEFs) for individual compounds were established/extrapolated from the database of many in-vivo studies. Since the 1980s, the TEF concept has been developed and refined (Safe *et al.*, 1985; Safe, 1990; Ahlborg *et al.*, 1994; Van den Berg *et al.*, 1998). Current TEF values were reevaluated recently using a refined TEF database (Haws *et al.*, 2006; Van den Berg *et al.*, 2006).

TEQ is defined by the sum of concentrations of dioxin-like compounds multiplied by their TEF values. A limitation of the concept is the additivity model being used, but its major advantage is the transformation of data on chemical concentration of complex mixtures into a single TCDD-like activity of the mixture. Many experimental studies with complex mixtures have confirmed that the TEQ approach is consistent with an additive model, although some deviations from additivity are observed. Another disadvantage is that the potential toxic and carcinogenic effects of non dioxin-like-PCBs (NDL-PCBs) are not included in this concept; high levels of NDL-PCBs may even suppress AhR-mediated toxicity, and thus act as antagonists.

Importantly, studies of carcinogenic and tumour-promoting activity were accounted for in the refined TEF database. Based on the TEF approach, carcinogenic hazard in humans may only be identified for DL-PCBs. The current TEF values for the PCB congeners included in the TEF concept are presented in Section 1, Table 1.4.

(c) Validation in experimental systems

AhR activation by DL-PCBs has been reported in many studies in vitro and in vivo, including comparative toxicogenomic analyses in primary human, monkey, and rodent hepatocytes (Silkworth *et al.*, 2005; Westerink *et al.* 2008). In a comparative in-vitro study in primary cultures of human and rat hepatocytes exposed to TCDD or PCB-126 at various concentrations for 48 hours, dose–responses and relative effective potencies (REP-values) were calculated for induction of CYP1A1 and other AhR-responsive genes (Carlson *et al.*, 2009). Previously, Silkworth *et al.* (2005) found that human cells are about 10–1000 times less sensitive to TCDD, PCB-126, and Aroclor 1254 than are rat and monkey cells.

Importantly, the newly calculated rat–human interspecies relative potency factors for PCB-126 were more than 100 times lower than the current rodent-derived value (Silkworth *et al.*, 2005).

These and other studies showed a relative insensitivity of the human AhR and human cells to PCB-126. In addition to a lesser potency of TCDD in human models (Haws *et al.*, 2006), lower potencies of PCB-126 might be due to species differences in relative intrinsic efficacy and/or species-specific differences in recruitment of transcriptional co-activators (Carlson *et al.*, 2009). In spite of the discrepancies between relative potencies of PCB-126 and TCDD in rodent and human liver cells, REP estimates based on induction of CYP1A1 or other AhR target genes might be relevant to evaluate the carcinogenic and hepatotoxic potential of TCDD and PCB-126 in humans.

The TEF approach and additivity concept were evaluated in 2-year cancer bioassays in groups of 53–55 female Harlan Sprague-Dawley rats receiving TCDD at a dose of 3–100 ng/kg bw per day, PCB-126 at a dose of 30–1000 ng/kg bw per day, 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) at a dose of 6–200 ng/kg bw per day, or a mixture of the three toxicants. Dose–response curves for hepatic, pulmonary, and oral mucosal neoplasms showed that carcinogenic effects could be predicted from the WHO TEF values (Walker *et al.*, 2005).

In a short-term study, female Harlan Sprague-Dawley rats were exposed for 13 weeks to toxicologically equivalent doses of four polychlorinated aromatic hydrocarbons based on their TEF: TCDD (100 ng/kg bw per day), PeCDF (200 ng/kg bw per day), PCB-126 (1000 ng/kg bw per day), or PCB-153 (1000 µg/kg bw per day) (Vezina *et al.*, 2004). The AhR agonists (TCDD, PeCDF, and PCB126) produced very similar global gene-expression profiles, while PCB-153 showed a different, non-AhR-mediated response. All four compounds induced significant liver hypertrophy. TCDD and PCB-126 were more effective in activating AhR-dependent gene expression and inducing hepatic hypertrophy than was PeCDF, although the administered doses of each compound were based on equal TEQ values. These data fitted perfectly with the TEF value for PCB-126 in rats. Nevertheless, the gene-expression data might not bear a direct relevance to carcinogenicity of the studied compounds (Vezina *et al.*, 2004).

Global gene expression was investigated in vitro in the contact-inhibited rat liver progenitor WB-F344 cells exposed to PCB-126 at a concentration of 100 nM, or TCDD at 1 nM, for 6, 24, and 72 hours (Faust *et al.*, 2013). AhR dependency was validated using both chemical inhibition of AhR and knockdown of the AhR or the aryl hydrocarbon receptor nuclear translocator (ARNT) using small interfering RNA (siRNA). Gene ontology analysis revealed that, apart from deregulation of drug and lipid metabolism, genes participating in regulation of the cell cycle and growth control, developmental and cancer pathways, cell–cell communication and adhesion were significantly affected. Importantly, transcriptional regulation mediated by PCB-126 was very similar to that induced by TCDD in rat liver in vivo (Vezina *et al.*, 2004), and in rat liver progenitor WB-F344 cells. [Nevertheless, the relevance of these data to human carcinogenesis remained limited due to the species-specific pattern of AhR-dependent gene expression (Dere *et al.*, 2011).]

4.3.2 Cell death and proliferation

(a) Apoptosis, cell proliferation, and cell cycle control

(i) Apoptosis

DL-PCBs and NDL-PCBs have been shown to suppress DNA damage-induced apoptosis in vitro (Knerr & Schrenk, 2006; Al-Anati *et al.*, 2010).

PCB-28, PCB-101, and PCB-187 inhibited ultraviolet irradiation-induced apoptosis in hepatocytes from male Wistar rats pre-exposed to ultraviolet radiation before being treated with PCBs for 12 hours. A statistically significant suppression of apoptosis was found after the treatment with PCB-28 at 1 nM, PCB-101 at 10 nM, or PCB-187 at 1 μM (Bohnenberger *et al.*, 2001; Schrenk *et al.*, 2004).

PCB-126, and several NDL-PCBs (concentration range, 0.01–10 μM), attenuated the TP53-mediated apoptotic response via phosphorylation of the regulatory protein MDM2 in human hepatoma HepG2 cells (Al-Anati *et al.*, 2009). PCB-28, PCB-101, and PCB-153 reduced benzo[*a*]pyrene-induced phosphorylation of MDM2, and amplified the benzo[*a*]pyrene-induced TP53-dependent apoptotic response; however, benzo[*a*]pyrene-induced apoptosis was inhibited. Reduced levels of phosphorylated forkhead family transcription factor FOXO3a [FOXO3] were also reported after treatment with NDL-PCBs (Al-Anati *et al.*, 2010). FOXO3a probably functions as a trigger for apoptosis through expression of genes necessary for cell death. Thus NDL-PCBs may also inhibit benzo[*a*]pyrene-induced apoptosis by preventing phosphorylation of FOXO3a (Al-Anati *et al.*, 2010).

(ii) Cell proliferation

Cell proliferation can be caused either by cytotoxicity/injury and regenerative proliferation, or by a sustained increase in proliferation. It is mediated via several signal-transduction pathways leading to pro-proliferative changes in gene expression (controlled by specific transcription factors, such as AhR, CAR, NF-κB or AP-1). These events may drive genotoxic and nongenotoxic processes associated with tumour promotion and progression. PCBs have been reported to induce such proliferative events in a series of experimental in-vitro and in-vivo models (Tharappel *et al.*, 2002; Marlowe & Puga, 2005; Puga *et al.*, 2009).

CAR is known to control the hepatic expression of detoxification enzymes and to induce sustained cell proliferation in the liver. *Ortho*-substituted PCBs induce expression of CYP isoenzymes (see Section 4.1.3) via CAR (Muangmoonchai *et al.*, 2001). The activation of CAR-dependent gene expression by NDL-PCBs in vivo has been observed, e.g. in rat liver after 28-day exposure to PCB-180 (Roos *et al.*, 2011), or in the liver of immature, ovariectomized C57BL/6 mice treated with PCB-153 (Kopec *et al.*, 2010). Using a range of genetically engineered human cell models derived from liver, lung, and colon tissues, it has been shown that several NDL-PCBs, such as PCB-99, PCB-138, PCB-153, PCB-180 or PCB-194, may activate CAR-controlled reporter vectors, as well as PXR reporters, in a tissue-specific manner (Al-Salman and Plant, 2012). [The Working Group was aware that the relevance to human risk of CAR-driven hepatocarcinogenic effects seen in rodents has been questioned (Holsapple *et al.*, 2006).]

In the 13-week study by Vezina *et al.* (2004), modulation of global gene expression was analysed in liver of female rats given PCB-153 at a dose of 1000 μg/kg bw per day. In addition to CYP2B1 and CYP2B2, PCB-153 also modulated the expression of anti-apoptotic genes (*Bcl2* and *Wee1* were downregulated), and other genes associated with liver injury. PCB-153 selectively enhanced expression of the cAMP response element modulator (CREM), which is a signature response to liver regeneration after hepatocyte injury.

In an initiation–promotion study in female Sprague-Dawley rats, an increase in the frequency of several preneoplastic foci, and increased NF-κB and AP-1 binding activities were observed in the liver of rats given PCBs (Tharappel *et al.*, 2002). Although cell proliferation was not affected by PCB-153, apoptotic indexes were decreased in focal hepatocytes by PCB-153. The induction of altered hepatic foci appeared to be related to compensatory cell proliferation in rats treated

with PCB-77, while inhibition of apoptosis appeared to be important for rats treated with PCB-153 (Tharappel *et al.*, 2002). In a subsequent study, a single dose of PCB-153 (at 150 or 300 µmol/kg bw), but not PCB-77, induced hepatocyte proliferation and hepatic NF-κB activation in male Sprague Dawley rats (Lu *et al.*, 2003). Comparison of the effects of PCB-153 in wild-type mice and in mice deficient in the NF-κB p50 subunit suggested possible involvement of NF-κB in PCB-153-modulated cell proliferation and apoptotic changes (Lu *et al.*, 2004). Absence of the NF-kB p50 subunit inhibited the promoting activity of PCB-153, as illustrated by the NF-κB knockout study in mice treated with diethylnitrosamine/PCB-153. Taken together these data implicate a possible role for oxidative stress-mediated activation of specific transcription factors, such as NF-κB, as a possible mode of action for NDL-PCBs (Glauert *et al.*, 2008).

Brown *et al.* (2007) have reported a correlation between incidence of tumours of the liver and increased activity of mixed function oxidases and increased expression of proliferating cell nuclear antigen (the indicator of cell proliferation) in Sprague-Dawley rats exposed to repeated doses of Aroclor mixtures for 24 months. [From these data, it was not clear to which class of PCB congeners (DL- or NDL-PCBs) the effects could be attributed.]

In nontumorigenic human mammary epithelial MCF-10A cells, PCB-153 at a concentration of 1–15 µM, Aroclor 1254 and 2-(4-chlorophenyl) benzo-1,4-quinone increased levels of reactive oxygen species, and caused cell-cycle delay and growth inhibition by suppressing levels of cyclin D1 (Venkatesha *et al.*, 2008, 2010; Chaudhuri *et al.*, 2010).

Further studies also examined the role of AhR in PCB-mediated deregulation of cell proliferation. Activation of AhR is known to cause a delay in cell-cycle progression in several cancer cell lines, models of differentiated cells (e.g. rodent hepatoma cells), and in primary rodent hepatocytes (Elferink, 2003; Marlowe & Puga, 2005). However, AhR ligands have been found to elicit opposite effects in liver progenitor cells: induction of cell proliferation in contact-inhibited rat liver progenitor cells in vitro by DL-PCBs was reported to be an AhR-dependent process (Vondráček *et al.*, 2005). Like TCDD, PCB-126 at 100 pM, 4′-OH-PCB-79 (a metabolite of coplanar PCB-77) at 1 µM, or PCB-105 (mono-*ortho*-chlorinated congener) at 10 µM increased the percentage of cells in S-phase and the total number of cells. In contrast, the NDL-PCBs and their metabolites had no effect on cell proliferation at concentrations up to 10 µM. Only PCB-126 (AhR-activating), and not PCB-153 (not AhR-activating), upregulated levels of cyclin A and D2 protein (Vondráček *et al.*, 2005). The proliferative effects of PCB-126 were further potentiated by tumour necrosis factor-α (Umannová *et al.*, 2007).

(iii) DNA synthesis

The rate of DNA synthesis in altered hepatic foci and in tumours in PCB-treated rats and mice was studied by Tharappel *et al.* (2002), who gave rats DEN at a dietary concentration of 150 mg/kg followed by four biweekly intraperitoneal injections of PCB-77 or PCB-153 at a dose of 100 or 300 µmol/kg bw. Rats were given bromodeoxyuridine (BrdU) in Alzet osmotic pumps for the measurement of DNA synthesis in focal and nonfocal hepatocytes. PCB-77 increased the BrdU labelling indexes in GSTP-positive foci and in normal hepatocytes, but PCB-153 did not. Similarly, PCB-153 did not influence the BrdU labelling index in DEN-initiated hepatic tumours in mice (Glauert *et al.*, 2008). Haag-Grönlund *et al.* (2000) found that weekly subcutaneous injections of PCB-118 at doses of 10–10 000 µg/kg bw did not increase BrdU labelling in focal hepatocytes after 20 weeks, but that PCB-118 at a dose of 10 000 µg/kg bw increased the BrdU labelling index after 52 weeks.

(b) Cell–cell communication

Several studies have demonstrated that PCBs can inhibit gap-junctional intercellular communication (GJIC) both in vivo (Krutovskikh *et al.*, 1995; Bager *et al.*, 1997) and in vitro in rat liver epithelial cells, mouse and rat hepatocytes, human keratinocytes, and normal human breast epithelial cells (Ruch & Klaunig, 1986; Swierenga *et al.*, 1990; Hemming *et al.*, 1991; Kang *et al.*, 1996). The *ortho*-substituted PCBs were potent inhibitors of GJIC at low micromolar concentrations, while the coplanar PCBs did not inhibit GJIC after a single dose (Machala *et al.*, 2003). The assay for GJIC inhibition showed good predictability for tumour promotion of *ortho*-substituted PCBs. Recently, inhibition of GJIC has been confirmed using single doses of ultrapure NDL-PCB congeners (Hamers *et al.*, 2011).

Different cell- and connexin-specific mechanisms of action probably account for the inhibitory effects of PCBs on GJIC. Of the NDL-PCBs, PCB-153 decreased the number of gap-junction plaques, and decreased levels of connexin 43 (constitutive protein of gap junctions) in liver epithelial cells. PCB-153 enhanced proteasomal and lysosomal degradation of connexin 43 and inhibited trafficking of connexin 43 to the plasma membrane (Šimečková *et al.*, 2009a). In contrast, inhibition of GJIC by AhR ligands (i.e. DL-PCBs such as PCB-126) seems to proceed mainly through downregulation of mRNA of connexin 32 in hepatocyte-derived models (Herrmann *et al.*, 2002).

(c) Other cellular mechanisms relevant to PCB-induced carcinogenesis

NDL-PCBs have been shown to elicit additional nongenomic effects on membrane-associated proteins, which are closely related to tumour promotion and progression.

PCB-153 was found to increase the incidence of glutamine synthetase-positive tumours of the liver in male B6129sf2/J mice, and almost 90% (34 out of 38) of all tumours from mice treated with PCB-153 contained mutations in the β-catenin gene (*Catnb*), compared with ~45% (17 out of 37) of tumours in the control group. Tumours containing mutations of Ha-*ras* [*Hras*] and B-*raf* [*Braf*] were rare and not significantly different between treatment groups. Exposure to PCB-153 appeared to strongly select for *Catnb*-mutated, glutamine synthetase-positive tumours of the liver in mice (Strathmann *et al.*, 2006).

In the rat liver progenitor WB-F344 cell line, PCB-153 was found to decrease levels of several proteins at adherens junctions involved in cell–cell communication and intracellular signalling, including E-cadherin, β-catenin, and plakoglobin (Šimečková *et al.*, 2009b). Such mechanisms may be involved in the effects of NDL-PCBs, contributing to promotion of tumours.

Oral administration of dioxin-like PCB-126, mono-*ortho*-substituted PCB-118, and non-dioxin-like PCB-153 differentially altered expression of the tight junction proteins claudin 5, occludin, and ZO-1 in brain capillaries in C57/B16 mice. These alterations were associated with increased permeability of the blood–brain barrier. Most importantly, exposure to individual PCB congeners enhanced the rate of formation and progression of brain metastases by luciferase-tagged melanoma cells (Seelbach *et al.*, 2010).

As vascular endothelial cells create a selective barrier to the passage of cancer cells, it is of interest to note that non-dioxin-like PCB-104 induced endothelial hyperpermeability of human microvascular endothelial cells HMEC-1 and trans-endothelial migration of human breast cancer cells MDA-MB-231; these effects were associated with overexpression of vascular endothelial growth factor (Eum *et al.*, 2004).

Structurally different PCBs may induce proinflammatory mediators, which further contribute to metastasis. PCB-77, PCB-104 and PCB-153 induced expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and monocyte

chemoattractant protein-1 (MCP-1) in the liver, lung, and brain of male C57Bl/6 mice. PCB-77 and PCB-104 also increased levels of matrix metalloproteinase-7 (MMP-7) mRNA in the liver and brain (Sipka *et al.*, 2008).

The mixture of seven NDL-PCBs (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180, and PCB-209) increased cell motility of human non-metastatic MCF-7 cells and human metastatic breast cancer MDA-MB-231 cells in vitro via production of reactive oxygen species, and activation of the Rho-associated kinase (ROCK). In a follow-up study in vivo, the PCB mixture enhanced the capability of metastatic breast cancer cells to metastasize to bone, lung, and liver (Liu *et al.*, 2010).

To explore the possible effects of PCBs on telomeres and telomerase, human skin keratinocytes were exposed to a synthetic mixture of volatile PCBs, or the prominent airborne PCB congeners, PCB-28 or PCB-52, for up to 48 days (see also Section 4.2.2b). The PCB mixture and the two congeners significantly inhibited telomerase activity from day 18, while telomere length was reduced by PCB-52 from day 18, and by PCB-28 and by the mixture from day 30 onwards (Senthilkumar *et al.*, 2011).

New bioanalytical tools (e.g. transcriptomics) applied in human, animal, and in-vitro studies might improve the ability to predict the potential carcinogenicity of chemicals by elucidation of similar mechanisms (Guyton *et al.*, 2009). Several analyses of global gene expression in rodent models included identification of the effects of DL-PCBs, especially PCB-126, on pathways related to carcinogenicity.

4.3.3 Endocrine disruption

Extensive data indicate an association between exposure to PCBs and endocrine disruption. The effects include primarily interference with the function of sex hormones, i.e. estrogens and androgens, and their receptors (reviewed by Bonefeld-Jørgensen, 2010; Bonefeld-Jørgensen *et al.*, 2011; Crinnion, 2011; Fucic *et al.*, 2012). In addition, PCBs are able to bind to thyroxine transport protein (TTR), human thyroxine-binding globulin, and thyroid-hormone receptors (reviewed by Cheek *et al.*, 1999; Kawano *et al.*, 2005; Grimm *et al.*, 2013); disruption of the thyroid-hormone system was observed up to 30 years after exposure (Masuda, 2001). Furthermore, PCBs affect hormone-metabolizing enzymes, e.g. of the CYP1, CYP2, CYP3A subfamilies, and uridine-diphosphate-glucuronyl transferase, iodothyronine deiodinase, and sulfotransferase (Brouwer *et al.*, 1998).

OH-PCB and PCB-catechol and PCB-quinone metabolites formed by CYP and other oxidative enzymes have been implicated as direct or indirect endocrine-disrupting agents. The interactions found depended upon the position of hydroxylation, as well as the proximity of chlorine substitutents and the substitution pattern. Some OH-PCBs are retained in blood because they bind to transthyretin (TTR) (Lans *et al.*, 1993). Several OH-PCBs, PCB-catechols and PCB-quinones interact with estrogen receptors and other cellular receptors as agonists or antagonists (Garner *et al.*, 1999). Other OH-PCBs inhibit human estrogen sulfotransferase, thyroid hormone sulfotransferase and phenol sulfotransferases, with inhibitory potencies (IC_{50}) ranging from less than nM to low μM (Schuur *et al.*, 1998a). Species differences in the protein structures of these sulfotransferases are such that there are differences in potency of inhibition of the corresponding sulfotransferases from other species such as fish (Wang & James, 2007). The human sulfotransferase enzymes are more potently inhibited by OH-PCB than those of other species (see details below).

(a) Humans

(i) Effects on sex hormones and their receptors

Serum samples were collected from male residents of an area in eastern Slovakia with extensive environmental contamination from a former PCB-production site, as well as from a neighbouring non-industrial region. The highest quartile of PCB concentrations was significantly associated with reduced estrogen receptor-mediated activity, and a negative correlation was observed between total estrogenic activity and dioxin-like activity. No correlation was found between E_2 [17beta-estradiol] concentrations and total PCB concentrations (R_s = 0.078). E_2 was largely responsible for the estrogenic activity identified in total serum extracts (Plísková *et al.*, 2005).

PCB-induced endocrine dysfunction related to the hypothalamic–pituitary–gonadal axis was evaluated in a birth-cohort study in Germany, initiated in 2000. Healthy mother–infant pairs were recruited in the industrialized city of Duisburg. Dioxins, DL-PCBs, and six indicator PCBs (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180) were measured in maternal blood during pregnancy and in breast milk. Concentrations of testosterone and estradiol were measured in maternal and cord serum of 104 mother–infant pairs. Linear-regression analysis was used to describe the association of PCBs in maternal blood or milk with the serum concentrations of the sex steroids, after adjustment for confounding. Median concentrations for the sum of indicator PCBs were 149 ng/g in maternal blood fat and 177 ng/g in milk fat. Typically, reduction in testosterone concentrations was more pronounced in the cord serum of female babies. In contrast, male babies showed a stronger reduction in estradiol concentrations. The only statistically significant reduction associated with the six indicator PCBs was for testosterone in girls (means ratio, 0.76; 95% CI, 0.61–0.96) (Cao *et al.*, 2008).

Serum concentrations of testosterone in relation to concentrations of PCBs were investigated in an adult Native American (Mohawk) population. Fasting serum samples were collected from 257 men and 436 women, and analysed for the presence of 101 PCB congeners, and for testosterone, cholesterol, and triglycerides. The associations between testosterone and tertiles of PCB concentrations in serum (both adjusted for wet weight and lipid) were assessed by use of a logistic regression model, controlled for age, body mass index (BMI), and other factors. The lowest tertile was taken as the reference level. Testosterone concentrations in men were inversely correlated with total PCB concentration in serum, and with concentrations of the congeners PCB-74, PCB-99, PCB-153, and PCB-206, but not PCB-52, PCB-105, PCB-118, PCB-138, PCB-170, PCB-180, PCB-201, or PCB-203. Testosterone concentrations in women were much lower than in men, and not significantly correlated with serum concentrations of PCBs (Goncharov *et al.*, 2009).

A possible correlation between exposure to PCBs and testosterone concentrations was studied in 834 men from Eastern Slovakia (age, 21–78 years; median age, 48 years), of whom 432 were from a highly polluted area, and 402 were from an area with background pollution. Serum concentrations of 15 PCB congeners were measured by gas chromatography/mass spectrometry, and total testosterone was determined immunochemically (electrochemiluminescence). Correlation coefficients for each PCB congener and for the total of 15 PCBs (Σ15PCBs) with testosterone were determined. The full cohort of 834 men (median concentration of Σ15PCBs, 885 ng/g lipid) showed a highly statistically significant negative correlation between testosterone concentration and age (r = 0.303; $P < 0.0001$). A significant negative correlation ($P < 0.05$) with testosterone concentration was seen only for two mono-*ortho*-congeners, i.e. PCB-105 and PCB-118. No significant correlations were found in the subcohort of 444 men

in a narrower age range (41–55 years), in which there was no effect of age on testosterone concentrations (Langer *et al.*, 2010).

A follow-up study by the same authors included 429 men (age, 41–55 years) from a highly polluted area in Eastern Slovakia. For all subjects, the serum concentrations of 15 PCB congeners and several other chemicals were measured by gas chromatography/mass spectrometry, and total testosterone in serum was determined by electrochemiluminescence immunoassay. Similarly to the previous analysis, there was no statistically significant correlation between Σ15PCBs and testosterone (Langer *et al.*, 2012).

The association of PCBs with sex-hormone concentrations in serum was assessed in 341 men from an infertility clinic in the USA, whose exposure levels to PCBs were comparable to those observed in the general population. In crude regression models, inverse correlations were found between serum concentrations of PCBs and steroid hormone-binding globulin (SHBG) and total and free testosterone. However, after adjustment for lipids, age, and body-mass index, nearly all the significant associations disappeared: an inverse correlation remained between PCB-118 and SHBG ($P < 0.01$), while those between DL-PCBs and SHBG and total testosterone, and between PCB-118 and total testosterone, were suggestive but not statistically significant (Ferguson *et al.*, 2012).

A few studies explored the relationship between levels of steroid hormones in consumers of contaminated fatty fish from the Great Lakes (Persky *et al.*, 2001; Turyk *et al.*, 2006; see below).

(ii) Effects on the thyroid-hormone system

In a study of more than 600 children in Germany, blood samples collected from 320 children showed a significant positive correlation between serum concentrations of PCBs and increased levels of thyroid-stimulating hormone (TSH), and a significant inverse correlation with free total thyroxine (T4), as was to be expected when TSH increases (Osius *et al.*, 1999).

Hagmar *et al.* (2001a) studied the relationship between the amounts of various organohalogenic compounds in fatty fish from the Baltic Sea and hormone levels in adult men who consumed these fish. Plasma samples from 110 men (43 from south-eastern Sweden, 67 from Latvia; age range, 23–79 years) who consumed up to 32 fish-meals per month were analysed for the presence of 18 PCB congeners, five OH-PCBs, and various other chemicals. In addition, plasma concentrations of follicle-stimulating hormone, luteinizing hormone, prolactin, plasma thyrotropin, free and total triiodothyronine (T3), free and total T4, and free testosterone were measured. After adjustment for age, no significant associations were found between any of these markers and any of the PCBs or OH-PCBs. However, a study among 182 fishermen's wives (age range, 23–46 years) from the east coast of Sweden, who had a median consumption of contaminated fatty fish from the Baltic Sea of two meals per month (range, 0–12 meals), found a significant inverse correlation between PCB-153 concentrations (range, 16–776 ng/g lipid) and total T3 levels in plasma, also after adjustment for age ($P < 0.001$) (Hagmar *et al.*, 2001b). An inverse correlation was also observed with total T4, which was borderline significant ($P = 0.07$).

Parallel to a larger investigation of consumption of contaminated fatty fish from the Great Lakes and effects on reproductive function, the association between PCB intake via consumption of fish and effects on thyroid and steroid hormones was studied in 178 men, and on thyroid hormones in 51 women (Persky *et al.*, 2001). Serum concentrations of PCBs and fish consumption were associated with significantly lower levels of T4 and a significantly lower free T4 index in women. Fish consumption, but not serum PCB concentration, was associated with a higher uptake of T3 in men. Results for TSH were inconsistent. Among men, there were significant

inverse associations for serum PCB concentration and fish consumption with SHBG-bound testosterone, but no association with SHBG itself, or with free testosterone. There were no significant overall associations for serum PCB concentration or fish consumption with estrone sulfate, follicle-stimulating hormone, luteinizing hormone, or dehydroepiandrosterone sulfate.

The relationsip between levels of steroid and thyroid hormones and total NDL-PCBs was investigated in 56 men who were frequent or infrequent consumers of fish from the Great Lakes (Turyk *et al.*, 2006). The men had consumed fish meals for 15–57 years. Significant inverse associations with serum PCB concentrations were found for T3, T4, TSH, and SHBG-bound testosterone, after adjustment for age, body-mass index, and use of medication. Follicle-stimulating hormone, luteinizing hormone, free testosterone, and SHBG were not associated with PCB concentrations in serum.

To assess the relationship between exposure to organochlorine compounds and thyroid function and neurodevelopment, a population-based birth-cohort study was conducted on the Faroe Islands (Denmark), where the regular consumption of PCB-contaminated fish is an important source of exposure (see Section 1.4.1). The study included 182 newborns who were followed up until age 54 months. PCB levels (calculated as the sum of congeners PCB-138, PCB-153, and PCB-180, multiplied by two) were measured in breast milk and maternal serum, and maternal blood and cord blood were collected for measurement of thyroid parameters. After covariate adjustments, consistent inverse and monotonic associations were observed between total PCB exposure and the resin T3 uptake ratio, a proxy measure of the binding capacity of T4-binding globulin sites that are not saturated with T4. The resin T3 uptake ratio is high in hyperthyroidism and low in hypothyroidism. No associations with other thyroid parameters (TSH, free T3, free T4) were observed (Julvez *et al.*, 2011).

In a study in 39 healthy pregnant women in the metropolitan area of Tokyo, Japan, associations were studied between in-utero exposure to PCBs or OH-PCBs and free T4 or TSH status in newborns. The concentration of total OH-PCBs and of OH-metabolites of PCB-187 in umbilical cord tissue was significantly correlated with higher levels of free T4 in heel-prick blood samples obtained from neonates aged 4–6 days. On the other hand, the concentration of total PCBs and of the congeners PCB-118, PCB-138, PCB-153, and PCB-180 showed no relationship with free T4 and TSH levels (Otake *et al.*, 2007).

In a study in 232 healthy mother–infant pairs recruited between 2000 and 2002 in the industrialized city of Duisburg, Germany, TSH, total T4, T3, free T4 and free T3 were measured in serum of the pregnant women and in cord serum (Wilhelm *et al.*, 2008). Blood levels (n = 182) of WHO 2005 TEQ (which includes PCDD/PCDF + PCBs) were in the range of 3.8–58.4 pg/g lipid (median, 19.3 pg/g lipid). The corresponding value for human milk (n = 149) was 2.6–52.4 pg/g lipid (median, 19.7 pg/g lipid). Multiple regression analyses did not detect any effects on thyroid hormones related to WHO 2005 TEQs in blood or milk of mothers and their newborns.

In a study among Inuit women and their infants, a positive correlation was found between concentrations of OH-PCBs and total T3 in plasma of 120 women at delivery ($\beta = 0.57$; $P = 0.02$). In umbilical cord plasma of 95 newborns, PCB-153 concentrations were negatively correlated with T4-binding globulin concentrations ($\beta = -0.26$; $P = 0.01$). No associations were observed between organochlorine contaminants and thyroid hormones in blood plasma collected from infants aged 7 months (Dallaire *et al.*, 2009).

(b) Experimental systems

(i) Effects on sex hormones and their receptors

Experimental animals in vivo

Groups of pregnant Wistar WU rats received a daily oral dose of 4-OH-2,3,3′,4′,5-pentachlorobiphenyl [4-OH-PCB-109] at 0.5 or 5.0 mg/kg bw, or Aroclor 1254 at 25 mg/kg bw, on days 10–16 of gestation. The diestrous stage of the estrous cycle was significantly prolonged in 75% and 82% of female offspring exposed to 4-OH-PCB-109 at the lower and higher dose, respectively, compared with 64% of Aroclor-exposed offspring. This effect resembled a state of pseudopregnancy. Plasma estradiol concentrations in female offspring were significantly increased (50%) in the proestrous stage after exposure to 4-OH-PCB-109 at the higher dose, while no effects on estradiol were seen in rats treated with Aroclor 1254 (Meerts *et al.*, 2004).

In the offspring (age, 17 weeks) of Sprague-Dawley dams treated intragastrically with PCB-77 at a dose of 250 ng/kg bw on days 13–19 post-conception, the concentrations of follicle-stimulating hormone, luteinizing hormone, and testosterone were similar to those in the controls (Wakui *et al.*, 2012).

In-vitro assays

In an in-vitro estrogen-reporter assay with T47 human breast-cancer cells, the less chlorinated congeners (PCB-28, PCB-52, PCB-66, and PCB-74) were estrogenic, while the more highly chlorinated congeners (PCB-138, PCB-153, PCB-170, PCB-180, PCB-187, PCB-194, PCB-199, and PCB-203) acted as anti-estrogens. Co-planar PCBs had no effect on estrogen-receptor activation in this assay (Plísková *et al.*, 2005).

Less chlorinated, *ortho*-substituted, non-co-planar PCBs were weakly estrogenic in some in-vitro assays. Results in MCF-7 human breast-cancer cells were generally consistent with, but not absolute in, the requirement for *ortho*-chlorine substitution and *para*-hydroxylation for estrogenic potency (Gierthy *et al.*, 1997).

In MCF-7 human breast-cancer epithelial cells, three abundant PCBs, i.e. PCB-138, PCB-153 and PCB-180, showed pleiotropic effects on the estrogen and androgen receptors. Slightly increased cell proliferation was observed at low PCB concentrations (1–10 nM) in cells co-treated with E_2 at 0.01 nM, while the PCBs significantly inhibited cell growth at higher concentrations (1 and 10 μM). In a reporter assay (ERE-*tk*-CAT analysis), the three congeners induced a significant decrease of ER-E_2-mediated CAT activity. PCB-138 had a dose-dependent antagonistic effect on androgen-receptor activity in transiently co-transfected Chinese hamster ovary cells, with an IC_{50} of 6.2 μM. Thus the three PCBs compete with the binding of two natural hormone-receptor ligands (Bonefeld-Jørgensen *et al.*, 2001). In reporter-based assay with LNCaP human prostate-cancer cells, the congeners PCB-42, PCB-128, PCB-138 and the Aroclor mixtures 1242, 1248, 1254, and 1260, showed antagonizing effects on androgen-receptor activity (Portigal *et al.*, 2002).

The effects of PCB-77, PCB-118, PCB-126, and PCB-153 (at 0.01–20 μg/mL) on the human prostatic carcinoma cell-line LNCaP were investigated in vitro. PCB-77 and PCB-126 reduced androgen-dependent prostate-specific antigen (PSA) secretion and LNCaP cell proliferation, and inhibited 5-α-reductase activity. PCB-118 and PCB-153 had no effect on 5-α-reductase, but showed a biphasic effect on LNCaP cell proliferation, with low concentrations (0.1–1 μg/mL) causing an increase, and higher concentrations (10–20 μg/mL) a significant reduction. Likewise, PCB-118 and PCB-153 enhanced PSA secretion at low concentrations and reduced it at higher concentrations. Since induction of ethoxyresorufin-O-deethylase (EROD) and inhibition of 5-α-reductase activity were not observed, these PCBs act through an AhR- and androgen-receptor-independent mechanism. The anti-androgenic effects of the *meta*- and *para*-substituted PCB-77 and PCB-126 are more pronounced than

those of *ortho*-substituted PCB-118 and PCB-153 (Endo *et al.*, 2003).

The estrogenicity of binary mixtures of the OH-PCBs 2,4,6-trichloro-4′-biphenylol (4′-OH-PCB-30) and 2,3,4,5-tetrachloro-4′-biphenylol (4′-OH-PCB-61), was examined in the MCF-7 focus assay and a competitive estrogen-receptor binding assay. Although the individual OH-PCBs were estrogenic in both assays, there was no synergy when they were combined at various concentrations as equimolar mixtures (Arcaro *et al.*, 1998). Likewise, the estrogenic activities of these two OH-PCBs were additive when tested as equimolar mixture in several systems (MCF-7 cells, MDA-MB-231 human breast-cancer cells, mouse uterus) at high and low levels of estrogen-receptor expression, confirming the lack of a synergistic effect (Ramamoorthy *et al.*, 1997).

PCB-138, PCB-153, and PCB-180, as well as other non-*ortho*- and di-*ortho*-substituted PCBs, were shown to interfere with the function of the androgen and estrogen receptors in vitro (Schrader & Cooke, 2003; Hjelmborg *et al.*, 2006). Similarly, some OH-PCBs showed estrogenic and/or anti-estrogenic effects (Jansen *et al.*, 1993; Rasmussen *et al.*, 2003).

PCB-54 was chosen as a prototypical *ortho*-substituted PCB to test the hypothesis that *ortho* substitution in the absence of *para*- or *meta*-substituted chlorines may lead to enhanced estrogenic activity. The results indicated that PCB-54 is estrogenic both in vitro in the MCF-7 cell-focus test, and in vivo in the rat uterotropic assay (Arcaro *et al.*, 1999). The estrogenic activity of PCB-54 in MCF-7 cultures was inhibited by the estrogen-receptor antagonist LY156758. Competitive binding assays with recombinant human (rh) estrogen receptor indicated that PCB-54 does not bind to rhERalpha or rhERbeta, but the 4-hydroxylated metabolite of PCB-54 does. This metabolite was also 10-fold more estrogenic than PCB-54 in the MCF-7 focus assay, but was not detected in the medium of MCF-7 cultures exposed to PCB-54. These results suggested that the estrogenicity observed in the human breast-cancer cells and the rat uterus may be due to (i) binding of an undetected metabolite of PCB-54 to the estrogen receptor; (ii) direct binding of PCB-54 to a novel form of the estrogen receptor; or (iii) an unknown mechanism involving the estrogen receptor (Arcaro *et al.*, 1999).

Evidence that PCB-77 can act as an estrogen – with effects mediated by the estrogen receptor– was based on results from a variety of assays, including those assessing binding to the receptor in a competitive binding assay (where PCB-77 at 700-fold molar excess inhibited [^{3}H]-estradiol binding to the estrogen receptor by 50%); regulation of gene expression from a transfected exogenous (ERE-*tk*-CAT) or endogenous (*pS2*) estrogen-regulated gene; regulation of cell growth in the estrogen-dependent human breast-cancer cell lines MCF-7 and ZR-75–1; and activity in the immature mouse uterine-weight bioassay in vivo. These data demonstrated that PCB-77 mimics estrogenic action at concentrations in the nanomolar range (292 ng/L), which is comparable to concentrations of PCBs found in human tissues (Nesaretnam *et al.*, 1996).

The estrogenic effects of PCBs may be mediated in part by their hydroxylated metabolites. Both the parent compound and the OH-metabolite show low affinities for both the α- and β-isoform of the estrogen receptor, which suggests that they have only weak activity as estrogen-receptor agonist or antagonist. However, PCBs and OH-PCBs may be indirectly estrogenic by inhibiting human estrogen sulfotransferase (hEST). When 31 OH-PCBs were tested for their inhibitory effect on hEST, hydroxylation of one of the phenyl rings appeared to increase the inhibitory effect in the order *para*-OH > *meta*-OH > *ortho*-OH. Indeed, various environmentally relevant OH-PCBs (e.g. 4-OH-2,3,3′,4′,5-pentachlorobiphenyl, 4-OH-PCB-109; and 4,4′-dihydroxy-3,3′,5,5′-tetrachlorobiphenyl, 4,4′-$(OH)_2$PCB-80) are very potent inhibitors of hEST. Since sulfation by this enzyme is an

important pathway for E_2 inactivation, inhibition of this metabolic step would lead to increased bioavailability of estradiol. This would explain the indirect estrogenicity of hEST inhibitors (Kester *et al.*, 2000).

A series of twelve PCBs were investigated for their ability to bind to the uterine estrogen-receptor protein, by use of a competitive equilibrium-binding assay with enriched cytosol-receptor preparations (0–40% ammonium sulfate fraction) from uteri of ovariectomized mice. PCBs that showed strong affinities generally possessed either single or multiple *ortho*-chlorine substituents. For OH-metabolites, *ortho*-chlorine substitution on the phenolic ring seemed less effective than on the nonphenolic ring. Thus 4′-OH-2,4,6-trichlorobiphenyl (4′-OH-PCB-30), which has two *ortho* chlorines and a *para* substituent, had the strongest binding affinity. For PCBs without *ortho* chlorines, the binding activity decreased 10–100-fold. PCBs that demonstrated appreciable receptor-binding activity were also active in vivo in stimulating an increase in uterine weight, while weak binders were inactive in this respect. The *ortho*-chlorine substitution appears essential in determining receptor-binding activity, probably because of decreased conformational flexibility due to restricted rotation about the inter-ring bond (Korach *et al.*, 1988).

The effects of structure and substituent position on the estrogenic and anti-estrogenic activities of various OH-PCBs were investigated in a series of assays. The presence of an *ortho* or *meta* substitution in the phenolic ring had minimal effects on estrogenic activity, while the 2,4,6-trichloro- and 2,3,4,6-tetrachloro configuration in the non-phenolic ring were required for this response. Substitution in the phenolic ring had no effect on anti-estrogenic activity (Connor *et al.*, 1997).

In-vitro toxicity profiles were determined for 24 NDL-PCBs with respect to 10 different mechanisms of action. All NDL-PCBs antagonized androgen-receptor activation; none were androgenic. Less chlorinated NDL-PCBs (PCB-19, PCB-28, PCB-47, PCB-51, PCB-53, PCB-100, PCB-104, PCB-136) were weak estrogen-receptor agonists. More highly chlorinated NDL-PCBs (PCB-138, PCB-153, PCB-170, PCB-180, PCB-190) were weak estrogen-receptor antagonists; several inhibited estradiol-sulfotransferase activity by > 50% (PCB-28, PCB-47, PCB-51, PCB-53, PCB-100). On the basis of hierarchical analysis of the toxicity profiles, three separate clusters of NDL-PCBs and a fourth cluster of reference DL-PCBs could be distinguished. The indicators PCB-28, PCB-52, PCB-101, PCB-118, PCB-138, PCB-153, and PCB-180 contributed most to the anti-androgenic, anti-estrogenic, anti-thyroidal, tumour-promoting, and neurotoxic potencies calculated for PCB mixtures reported in human samples, while the most potent AhR-activating DL-PCB, PCB-126, contributed at most 0.2% to any of these calculated potencies. It was suggested that PCB-168 should be added to the list of indicator congeners, given its relatively high abundance and its anti-androgenic and TTR-binding properties (Hamers *et al.*, 2011).

(ii) Effects on the thyroid-hormone system

Experimental animals in vivo

Marmoset monkeys were treated with oral doses of PCB-77 at 0.1, 1, or 3 mg/kg bw, twice per week, for 18–23 weeks. Histological examination of the thyroid gland showed dose-dependent hyperplasia of follicular cells, which was associated with various changes in thyroid function. The average serum concentrations of T4 during the treatment period were reduced by 35% in monkeys at 0.1 mg/kg bw, 81% at 1 mg/kg bw, and > 99% at 3 mg/kg bw. A reduction in serum concentrations of T_4 was observed from 2 weeks and throughout the entire treatment period (18–23 weeks), and was reflected in a decrease in the free T4 index in the groups at 1 and 3 mg/kg bw. Serum T3 concentrations were reduced in the group at 3 mg/kg bw within 2

weeks. Concentrations of TSH were increased in the group at the highest dose as a feedback response to the strongly reduced serum T4 concentrations (van den Berg *et al.*, 1988).

Pregnant Wistar WU rats were given Aroclor 1254 as daily oral dose at 5 or 25 mg/kg bw on days 10–16 of gestation to determine effects on thyroid-hormone concentrations in plasma and brain, on peripheral thyroid-hormone concentrations, and on peripheral thyroid-hormone metabolism in fetal and weanling rats. Maternal exposure to Aroclor 1254 significantly reduced fetal (day 20 of gestation) and neonatal (postnatal day 4) plasma concentrations of total T4 and free T4. These effects were less pronounced in offspring at age 21 days and absent at 90 days. T3 concentrations in brain tissue in the exposed fetuses were significantly decreased relative to controls, but only in the group at the lower dose. On postnatal day 21, T4 concentrations had significantly decreased in the forebrain of female weanling rats from the group at the higher dose, but no reductions were seen in male or female neonates. The deiodination of T4 to T3 was significantly increased in fetal forebrain homogenates at both doses. No alterations in thyroid-hormone metabolism were seen in forebrain homogenates from adult offspring exposed pre- and postnatally to Aroclor 1254. Accumulation of the PCB metabolite 2,3,3′,4′,5-pentachloro-4-biphenylol [4-OH-PCB-109] was observed in fetal plasma and forebrain tissue on day 20 of gestation, and in neonatal and weanling plasma on postnatal days 4, 21, and 90 (Morse *et al.*, 1996).

In groups of Sprague-Dawley rats given two or five weekly intraperitoneal injections of PCB-126 (0.2 mg/kg bw) or PCB-114 (20 mg/kg bw), total T4 concentrations in serum were lower than those in the controls. The expression of TTR was significantly higher in the PCB-treated group than in the control group (Han *et al.*, 2010).

Reduced thyroid-hormone levels were found in serum of Sprague-Dawley rats treated with $MeSO_2$ metabolites of the following PCB congeners: 3-$MeSO_2$-2,2′,3′,4′,5,6-hexachlorobiphenyl [5′-$MeSO_2$-PCB-132]; 3-$MeSO_2$-2,2′,3′,4′,5,5′-hexachlorobiphenyl [3′-$MeSO_2$-PCB-141]; 3-$MeSO_2$-2,2′,4′,5,5′,6-hexachlorobiphenyl [5-$MeSO_2$-PCB-149] and 4-$MeSO_2$-2,2′,4′,5,5′,6-hexachlorobiphenyl [4-$MeSO_2$-PCB-149]. These $MeSO_2$-PCBs are found in human milk, liver, and adipose tissue. All four metabolites (20 µmol/kg bw, intraperitoneal injection, once per day, for 4 days) reduced the serum concentration of total T4 by 22–44%, on days 2, 3, 4 and 7 after the last dose. Concentrations of total T3 were reduced by 37% on day 7 after treatment with 4-$MeSO_2$-PCB-149. A 30% increase in thyroid weight was seen after treatment with 3′-$MeSO_2$-PCB-141. These data suggest that these 3- and 4-$MeSO_2$ metabolites act as endocrine disrupters, but probably through different mechanisms (Kato *et al.*, 1998). A similar study was conducted with the *meta*-$MeSO_2$ metabolites of tetra- and pentachlorinated biphenyls: 3-$MeSO_2$-2,2′,4′,5-tetraCB [3′-$MeSO_2$-PCB-49], 3-$MeSO_2$-2,3′,4′,5-tetraCB [3-$MeSO_2$-PCB-70], 3-$MeSO_2$-2,2′,3′,4′,5-pentaCB [3′-$MeSO_2$-PCB-87], 3-$MeSO_2$-2,2′,4′,5,5′-pentaCB [3′-$MeSO_2$-PCB-101], and the *para*-$MeSO_2$-metabolite 4-$MeSO_2$-2,2′,4′,5,5′-pentaCB [4′-$MeSO_2$-PCB-101]. The data showed that all five $MeSO_2$-PCBs influence thyroid-hormone metabolism (Kato *et al.*, 1999). A further study by this group demonstrated that the *meta*-$MeSO_2$ metabolites of PCB-49, PCB-70, PCB-87, PCB-101, PCB-132, PCB-141, PCB-149 [3′-$MeSO_2$-PCB-49, 3-$MeSO_2$-PCB-70, 3′-$MeSO_2$-PCB-87, 3′-$MeSO_2$-PCB-101, 5′-$MeSO_2$-PCB-132, 3′-$MeSO_2$-PCB-141, 5-$MeSO_2$-PCB-149] and the *para*-$MeSO_2$ metabolite of PCB-101 [4′-$MeSO_2$-PCB-101] induced hepatic microsomal UDP-glucuronosyl transferase (UDP-GT) in male Sprague-Dawley rats. The increase in hepatic glucuronidation of T4 after the administration of the eight test compounds was the probable cause of the reduced serum concentration of T4 (Kato *et al.*, 2000).

Thyroid hormone status and metabolism were studied in groups of pregnant Wistar WU rats given oral doses of 4-OH-2,3,3′,4′,5-pentachlorobiphenyl [4-OH-PCB-109] ([^{14}C]-labelled or unlabelled) at 5 mg/kg bw on days 10–16 of gestation. Fetuses were studied at days 17 and 20 of gestation. The test compound accumulated in the fetal compartment, with fetal/maternal ratios of 11.0, 2.6, and 1.2 in liver, cerebellum, and plasma, respectively, at day 20. Radiolabel was bound to plasma TTR in dams and fetuses. Fetal plasma concentrations of total T4 and free T4 were significantly decreased at days 17 and 20 of gestation (89% and 41%, respectively, at day 20), while fetal concentrations of TSH were increased more than twofold at day 20 of gestation. No effects were seen on T3 concentrations in fetal brain (Meerts *et al.*, 2002).

In a study to investigate the effects of PCBs on thyroid-hormone status, female Sprague-Dawley rats were given Aroclor 1254 at a dose of 4 mg/kg bw per day by gastric intubation for 14 days. To test underlying mechanisms, microsomal enzyme activities (CYP isozymes and UDP-GT, indicating metabolic activation and/or biliary clearance), ex-vivo binding of [^{125}I]-T_4 to plasma proteins (suggesting effects on peripheral thyroid-hormone transport), and light microscope morphology of the thyroid gland were studied. The extent of thyroid-hormone reduction (free T4 to 30% and total T4 to 60% of control) observed after exposure to Aroclor 1254 corresponded with a decrease in the ex-vivo binding of [^{125}I]-T_4 to plasma TTR, and with induction of the microsomal phase-I enzymes (ethoxy- and methoxy-resorufin dealkylase, EROD and MROD). The phase-II enzyme UDP-GT was moderately elevated. The thyroid morphology showed activation of the epithelium, but no degenerative alterations correlated with exposure to Aroclor 1254. The results suggested that the decrease in T4 is mainly due to disturbed serum transport, as a result of binding of Aroclor 1254 metabolites to TTR (Hallgren & Darnerud, 2002).

Miller *et al.* (2012) studied the effects of exposure to PCBs and PBDEs on T4 levels in rat offspring from day 6 of gestation until postnatal day 21. In male rat offspring, exposure to PCBs or PBDEs at a dose of 1.7, 5, 10, 20, 40, or 60 µmol/kg bw per day induced equivalent and dose-dependent reductions in T4 from postnatal days 7 to 21. Exposure to equimolar mixtures of PCBs and PBDEs at a dose of 3.4, 10, 20, 40, or 80 µmol/kg bw per day additively reduced T4 levels during the exposure period. The effects on T4 levels were similar in males and females.

In-vivo and ex-vivo systems

The OH-PCB metabolites 4-OH-PCB-69, 4-OH-PCB-106, and 4-OH-PCB-121 were tested for capacity to disrupt the thyroid-hormone system via proliferation of thyroid hormone-dependent rat-pituitary GH3 cells. Growth of GH3 cells was stimulated by all three 4-OH-PCBs (Ghisari & Bonefeld-Jørgensen, 2005). These OH-PCBs were previously reported to bind to the thyroid receptor and to thyroid-hormone transport proteins (Cheek *et al.*, 1999).

PCBs are the most concentrated class of pollutant found in polar bears (*Ursus maritimus*). In plasma samples collected from polar bears, no binding of [^{125}I]-T4 to TTR was observed. Incubation of these plasma samples with [^{14}C]-2,3,3′,4′,5-pentachloro-4-biphenylol [[^{14}C]-4-OH-PCB-109], a PCB metabolite with a higher binding affinity to TTR than the endogenous ligand T4 itself, resulted in competitive binding. Incubation of plasma with T4 at up to 1 mM (a concentration that is not physiologically relevant) did not result in any detectable competition. These results suggested that the binding sites on TTR for T4 in wild polar bears are completely saturated (Gutleb *et al.*, 2010).

Disruption of thyroid-hormone transport may be an important mechanism by which PCBs can alter thyroid-hormone homeostasis. In a systematic in-vitro study of PCB-binding to TTR, the role of *ortho* substitution was investigated in

more detail. PCBs that have only *ortho* substitution show significant binding activity. The congeners most closely resembling the diiodophenolic ring of T4, i.e. di-*meta*-substitution in one or both rings, showed the highest binding activity to TTR. Multiple *ortho* substituents decreased the binding activity of such congeners. PCBs with a single *meta* substitution in one or both rings resemble more closely the monoiodophenolic ring of T3, and showed significantly lower binding activity to TTR. This was consistent with the relatively low binding activity of T3 and the smaller size of chlorine compared with iodine. The addition of *ortho* substituents gave variable results, depending on their position (Chauhan *et al.*, 2000).

In in-vitro studies that assessed the effect of OH-PCBs on thyroid-hormone sulfation, the inhibition of sulfotransferase activity towards 3,3′-diiodo-thyronine (T2) appeared to be similar to that towards T3. Hydroxylated metabolites of PCBs strongly inhibited T2 sulfotransferase activity, the most potent inhibitor being 3-OH-2,3′,4,4′,5-pentachlorobiphenyl (3-OH-PCB-118). An important structural requirement for inhibition of T2 sulfotransferase by OH-PCBs is the presence of a hydroxyl group in the *para* or *meta* position, with *ortho*-OH-PCBs being much weaker inhibitors (Schuur *et al.*, 1998a, b).

4.3.4 Effects on the immune system

The effects of PCBs on several parameters related to the immune system have been reported for humans, and more extensively for experimental animals (reviewed by Tryphonas & Feeley, 2001).

(a) Adults

Immunomodulatory effects of PCBs have been reported in workers occupationally exposed to these chemicals, in humans following consumption of contaminated fish, and in populations accidentally exposed to PCBs and their heat-degradation products, PCDFs, and polychlorinated quarterphenyls (PCQ) via consumption of contaminated rice oil (the Yusho and Yucheng poisoning incidents). In addition, PCB exposure during prenatal and early life has been associated with incidence of infectious and allergic diseases in children, and alterations in immune-system development.

Lawton *et al.* (1985) tested 194 workers exposed occupationally (152 men, 42 women) to one or more of the Aroclors 1254, 1242, and 1016 in a capacitor plant factory for an average duration of 17 years. The results taken in 1976 were compared with those from the same workers taken in 1979, two years after discontinuation of all PCB use in 1977. Significantly increased levels of leukocytes, with a concomitant increase in levels of lymphocytes, monocytes and eosinophils, were observed when these workers were tested in 1976. Interestingly, the levels of circulating polymorphonuclear cells were reduced in the same workers. Similar, but not statistically significant, shifts in leukocyte levels were noted when testing was repeated in 1979. A positive association was observed between serum PCB concentrations and blood monocytes, and was reported to persist even 2 years after discontinuation of PCB use. [The Working Group noted that the extent to which PCB exposure compromises the immune system could not be estimated on the basis of immune-cell alterations, since measurement of functional immune parameters was not part of the study protocol.]

In contrast, a study by Emmett *et al.* (1988a, b) of 55 transformer repairmen working in a factory and exposed to Aroclors 1260 and 1242 did not report any significant exposure-related effects on the immune system. The percentage of workers with positive skin responses (delayed-type hypersensitivity) to mumps and trichophyton antigens was similar to that of 56 nonexposed workers.

Follow-up studies of the Yusho and Yucheng populations indicated that several immune-related parameters were disrupted in exposed

adults. These included a statistically significant decrease in serum levels of immunoglobulins A and M, reduced T-helper (Th) and increased T-suppressor cells (Ts) resulting in reduced Th:Ts cell ratio, persistent respiratory distress caused by Gram-negative bacilli-infected airways, and increased in-vitro lymphoproliferative responses of peripheral blood leukocytes to phytohaemaglutinin, concanavalin A, and pokeweed mitogens at 1 and 3 years after exposure. Furthermore, a reduced number of patients with positive skin-test reactivity to streptokinase/streptodornase antigens was observed at 1 year after exposure, and to tuberculin antigens at up to 4 years after exposure (Lü & Wu, 1985; Nakanishi *et al.*, 1985), while some other immunological effects persisted up to 30 years after exposure (Masuda, 2001).

Consumption of contaminated fish has been associated with some effects on the immune system. High consumption of fatty fish from the Baltic Sea correlated positively with B-cell numbers, but negatively with the percentage of cytotoxic ($CD8^+$) T-cells in 68 fishermen in Latvia (Hagmar *et al.*, 1995). [The significance of these observations was not clear, since no functional immune parameters were examined.]

Svensson *et al.* (1994) studied levels of leukocytes in a group of 23 men in Sweden who consumed high levels of fatty fish species from the Baltic Sea and compared results with 20 men who ate practically no fish. No effects were reported on leukocyte counts, the number of total lymphocytes or their subsets, or serum immunoglobulin levels. A marginal reduction in natural killer (NK) cell activity was reported for the fish-eating population. This was in agreement with the weakly negative correlation observed between NK cell numbers and blood concentrations of PCB-126 and PCB-118 in some of the same subjects tested 3 years previously.

(b) Children

Weisglas-Kuperus *et al.* (1995) studied children residing in the Netherlands and who were exposed, in utero and via breastfeeding, to ambient concentrations of PCBs. The study group consisted of 207 healthy mother–infant pairs. Prenatal exposure to PCBs was estimated by the sum of PCB-118, PCB-138, PCB-153, and PCB-180 (ΣPCB) in maternal and cord plasma, and in breastfed infants by the TEQ levels (based on 17 dioxins and 8 dioxin-like PCBs) in human milk. A higher prenatal PCB/dioxin exposure was associated with increased numbers of T lymphocytes bearing T-cell receptors of the gamma/delta type, increased cytotoxic T-cells at age 18 months in breastfed infants; higher prenatal and postnatal concentrations of PCB/dioxin was associated with reduced monocytes and granulocytes at age 3 months. In follow-up studies, statistically significant associations were observed between prenatal PCB exposure and increased number of lymphocytes, T-cells, and cytotoxic ($CD3^+CD8^+$) cells, memory ($CD4^+$ $CD45RO^+$) cells, T-cell receptor (TcR) $\alpha\beta^+$, and activated T-cell ($CD3^+$ HLA-DR^+) numbers in the toddlers.

Horváthová *et al.* (2011a, b) collected blood specimens from newborns, and infants aged 6 and 16 months, from two districts in Slovakia, Michalovce and Svidnik/Stropkov, that had respectively high and low environmental PCB contamination, and correlated blood PCB concentrations with lymphocyte-receptor expression. The percentages of lymphoid dendritic cells and naive/resting T lymphocytes were significantly increased at 6 months in the Michalovce area compared with those in cord blood samples ($P < 0.001$). Overall there was a positive correlation of terminally differentiated effector memory T-lymphocyte population with age, and a negative linear correlation for myeloid dendritic cells from birth to 6 months in both regions. The Michalovce samples indicated

significantly higher expression of memory T lymphocytes (at birth, 6, and 16 months), terminally differentiated effector memory T lymphocytes (at birth and at 6 months), and lymphoid dendritic cells (at 6 months) than in samples from Svidnik/Stropkov.

Jusko *et al.* (2012) investigated the effect of several PCB congeners on thymus volume in 1134 mother–infant pairs residing in eastern Slovakia. Samples of maternal and infant (age 6 and 16 months) blood were collected and analysed for 15 PCB congeners. Higher maternal concentrations of PCBs were associated with reduced thymus volume at birth, while maternal PCB concentration was not predictive of thymus volume in the infants aged 6 and 16 months.

In a subgroup of 331 children aged 7–10 years from the Hesse, Germany cohort, mean concentrations of PCBs were 0.50 µg/L, and this value was significantly associated with increased levels of serum immunoglobulin M (IgM) (Karmaus *et al.*, 2005).

Similar immune-related sensitivities in adolescence were reported by Van Den Heuvel *et al.* (2002) for a study in Flanders, Belgium. In this study, serum concentrations of PCB-138, PCB-153 and PCB-180, and combined serum dioxin-like activity as determined by AhR-mediated expression of a reporter gene luciferase, were measured in samples from boys and girls (aged 17–18 years) with certain immune-related respiratory complaints. A significantly negative correlation between the percentage of eosinophils and NK cells in peripheral blood and TEQ in serum ($P = 0.009$ and $P = 0.05$, respectively) was observed. Similarly, significant negative correlations were calculated between serum TEQs and levels of specific IgE antibodies to allergens (cat dander, house dust mite, and grass pollen), and the incidence of reported allergies of the upper airways. A significant positive correlation was observed between increased serum TEQs and increased serum IgA levels ($P = 0.05$).

(c) Non-human primates

Unlike all other experimental animal models in which exposure levels were high, the available studies in non-human primates used PCB doses that were relatively low (< 1 mg). Such studies have shown that non-human primates are more sensitive to the immune-related effects of PCBs than any other experimental animal tested. Alterations in the immune system and immunotoxicity were also reported after PCB exposure during prenatal or early life.

Thomas & Hinsdill (1978) investigated immunological parameters in groups of eight rhesus monkeys fed diets containing Aroclor 1248 at a dose of 0.1 or 0.2 mg/kg bw per day for 11 months. The reported immune-related effects were seen only at 0.2 mg/kg bw and included significantly reduced titres of antibodies to sheep red blood cells (SRBC) at weeks 1 and 12 after primary immunization, and decreased percentage of gamma-globulin after 20 weeks, compared with a control group of five monkeys. The response to tetanus toxoid was not affected by treatment. Reduced titres to SRBC were also reported in the single female cynomolgus monkey *(Macaca fascicularis)* treated with a PCB mixture with constituents similar to those ingested by Yusho patients, and containing predominantly penta- and hexachlorobiphenyls and no PCDFs, prepared from Kanechlor 400 and administered at 5 mg per day for 20 weeks (Hori *et al.*, 1982).

Differences in PCB-induced toxicity were investigated in cynomolgus *(Macaca fascicularis)* and rhesus *(Macaca mulatta)* monkeys (Tryphonas *et al.*, 1986; Arnold *et al.*, 1990). In these studies, groups of four cynomolgus and four rhesus monkeys ingested Aroclor 1254 in apple juice-gelatin-corn oil emulsion at doses of 0.00 (control) or 280 µg/kg bw per day for 12–13 months (cynomolgus monkeys) and 27–28 months (rhesus monkeys) respectively. The total serum IgM levels and titres to anti-SRBC (primary response) antigens were significantly

reduced in both species. Based on clinical and pathological findings, the rhesus monkeys were more sensitive to PCB-induced toxicities than the cynomolgus monkeys, although effects on the immune system were similar in both species.

A long-term study with Aroclor 1254 (Tryphonas *et al.*, 1989, 1991a, b; Arnold *et al.*, 1993, 1995) was of particular significance since it was the only long-term study in which low doses (range, 5–80 µg/kg bw per day) of commercial PCB mixtures were used. Immunological effects were reported after 23–25 months (phase I) (Tryphonas *et al.*, 1989), during which time a blood PCB pharmacokinetic equilibrium was established, and after 55 months (phase II) (Tryphonas *et al.*, 1991a, b). Testing at phase I detected significant shifts in Th and Ts lymphocyte subsets (decreased Th, increased Ts and decreased Th:Ts cell ratio) at 80 µg/kg bw per day, and significantly reduced titres in response to SRBC antigens (Tryphonas *et al.*,1989). The response to SRBC antigens was significantly reduced even at a dose of 5 µg/kg bw per day. These effects in monkeys were comparable to those reported for the Yucheng population at 1 and 3 years after exposure (Lü & Wu, 1985). Several significant immune-related parameters were affected in monkeys exposed continuously to Aroclor 1254 for 55 months (phase II). Effects included: a dose-related decrease in the anamnestic (IgM and IgG) response to SRBC antigens; a dose-related decrease in the lymphoproliferative response of leukocytes to the mitogens concanavalin A and phytohaemaglutinin, but not to pokeweed mitogen (mostly B-cell dependent); reduced monocyte activity (peak chemiluminescence after phorbol myristate acetate activation); significantly higher levels of serum complement (CH_{50}) activity across all treated groups compared with controls; a dose-related significant increase in thymosin α1 ($T\alpha_1$) levels in treated groups compared with controls; a significant but not dose-related increase in levels of interferon at the 20 and 80 µg/kg bw per day, with a significantly reduced interferon level at 40 µg/kg bw per day. Tumour necrosis factor (TNF) levels were not affected significantly by treatment (Tryphonas *et al.*, 1991a, b).

Hand-reared infant rhesus (*Macaca mulatta*) monkeys (age, 66 weeks) were treated with a mixture of PCB congeners at a dose of 7.5 µg/kg bw per day, which represents the approximate daily intake of a nursing infant whose mother's breast milk contained PCBs at a concentration of 50 ppb. The PCB congeners used for treatment were those commonly found in human breast milk in Canada. Treatment continued until the monkeys reached age 20 weeks. Significant treatment-related effects characterized by reduced antibody responses to SRBC antigens, and reduced levels of the HLA-DR cell surface marker were observed (Arnold *et al.*, 1999).

Groups of eight adult female rhesus monkeys were fed diets containing Aroclor 1248 at a concentration of 2.5 or 5.0 ppm for approximately 1.5 years (Allen & Barsotti, 1976). Six of the eight monkeys treated with Aroclor 1248 at 5.0 ppm, and all monkeys at 2.5 ppm were successfully bred after 6 months of exposure. There was one live infant born among monkeys at 5.0 ppm, and five infants born to monkeys at 2.5 ppm. Infants were permitted to nurse with their mothers. Three infants died within 8 months, after 44, 112 and 239 days, respectively. At necropsy, histopathological observations of the infant tissues included a near complete absence of thymocytes in the cortical and medullary areas of the thymus, extremely small lymph nodules of the spleen with inapparent germinal centres, and hypocellularity of the bone marrow.

(d) Rodents and rabbits

(i) Effects on the thymus

Commercial PCB mixtures

Thymic atrophy was detected in female White New Zealand rabbits fed diets containing Aroclor 1260 at a dose of 118 mg/kg bw per

day for 38 days, or Aroclor 1260 at a dose of 120 mg/kg bw per day for 28 days (Vos &Beems, 1971; Vos & Notenboom-Ram, 1972); in male White New Zealand rabbits fed Aroclor 1254 at a dietary concentration of 20, 45.8, or 170 ppm [0.92, 2.10 or 6.54 mg/kg bw per day] for 56 days (Street & Sharma, 1975); in male Fischer 344 rats given Aroclor 1254 at a dose of 10 or 25 mg/kg bw per day by gavage for 15 weeks (Smialowicz *et al.*, 1989); in female guinea-pigs fed Clophen A60 at a dietary concentration of 50 ppm for 49 days (Vos & van Driel-Grootenhuis, 1972) and in male Sprague-Dawley rats fed Aroclor 1262, 1254, or 1248 at 1% of the diet for 6 weeks. The severity of thymic atrophy was Aroclor 1254 = Aroclor 1248 > Aroclor 1262 (Allen & Abrahamson, 1973).

Thymic atrophy was not detected upon exposure to Aroclor 1248 when fed to female outbred albino mice (50, 100, 500 or 1000 ppm) for 3 to 5 weeks (Thomas & Hinsdill, 1978), or to Aroclor 1242 (167 ppm) fed to Balb/c mice (Loose *et al.*, 1979).

PCB congeners

Thymic atrophy characterized by reductions in cortical and medullary volume was also reported in weanling male and female Sprague-Dawley rats treated with feed containing individual PCB congeners for 13 weeks at the following concentrations: PCB-126, 0.1–100 ppb (0.01–7.4 µg/kg bw per day) (Chu *et al.*, 1994); PCB-153, 0.05–50 ppm (3.6–3534 µg/kg bw per day) (Chu *et al.*, 1996b); PCB-28, 0.05–50 ppm (2.8–3783 µg/kg bw per day) (Chu *et al.*, 1996c); and PCB-105, 0.05–50 ppm (3.9–4327 µg/kg bw per day) (Chu *et al.*, 1998). In contrast, PCB-77, PCB-118, and PCB-128 did not have any significant effects on the thymus when fed to weanling male and female Sprague-Dawley rats for 13 weeks at the following concentrations: PCB-77: 0.01–10 ppm (0.73–768 µg/kg bw per day) in males; 0.01–10 ppm (0.92–892 µg/kg bw per day) in females (Chu *et al.*, 1995); PCB-118: 0.01–10 ppm (0.66–683 µg/kg bw per day) in males; 0.002–2 ppm (0.17–170 µg/kg bw per day) in females; PCB-128: 0.05–50 ppm (4.5–4397 µg/kg bw per day) (Lecavalier *et al.*, 1997).

In male C57BL/6 (Ah+) and DBA/2 (Ah-) mice given intraperitoneal doses of PCB-77 (DL-PCB) or PCB-52 (NDL-PCB) at 0, 10, or 100 mg/kg bw per day, thymic atrophy was observed only in C57BL/6 mice treated with PCB-77 (Silkworth & Grabstein, 1982). The results suggested that PCB immunotoxicity in mice is mediated through the AhR, present only in the C57BL/6 mice.

(ii) Effects on humoral immunity

Commercial PCB mixtures

Several studies reported effects of PCBs on humoral immune reactivity. A significant reduction in production of antibodies to tetanus toxoid was noted in guinea-pigs fed Clophen A60 (Vos & van Driel-Grootenhuis, 1972), to keyhole limpet haemocyanin (KLH) in rats fed Aroclor 1254 (Exon *et al.*, 1985), and to SRBC using the plaque-forming cell assay in mice given Aroclor 1254 intraperitoneally (Wierda *et al.*, 1981; Loose *et al.*, 1979). Mice genetically engineered to be either aryl hydrocarbon-responsive (Ah^b/Ah^b) or non-responsive (Ah^d/Ah^d) did not exhibit the same sensitivity to PCB-induced suppression in the plaque-forming cell assay. For example, C57BL/6N (Ah^b/Ah^b) mice injected intraperitoneally with Aroclor 1254 at a dose of 250–750 mg/kg bw exhibited significant reductions in plaque-forming cell numbers after 5 days, compared with controls, while DBA/2N (Ah^d/Ah^d) mice failed to demonstrate any significant PCB-induced effects on plaque-forming cell numbers, compared with controls (Lubet *et al.*, 1986).

PCB congeners

Cotreatment of C57BL/6 B6 mice with PCB-153 and TCDD showed that PCB-153 partially antagonized TCDD-mediated immunotoxicity in various assays (Biegel *et al.*, 1989).

Individual congeners were also assessed for their immunotoxicity in AhR-responsive or AhR-non-responsive mouse models. Bandiera *et al.* (1982) reported that PCB-77 binds AhR with high affinity and causes severe suppression of the humoral antibody response in C57BL/6 B6 (Ah^b/Ah^b) mice. In comparison, PCB-77 exhibited lower binding affinity for AhR in DBA/2N (Ah^d/Ah^d) mice and did not cause any immune-related effects (Silkworth & Grabstein, 1982). In contrast, the di-*ortho*-substituted PCB-52 had weak AhR binding affinity and was not immunosuppressive in either mouse strain (Silkworth & Grabstein, 1982).

(iii) Effects on cellular immunity

The effects of PCBs were less pronounced on cellular immune responses than on humoral immune reactivity. Reduced skin reactivity to tuberculin was detected in female guinea-pigs fed Clophen A60 at 50 or 250 ppm for 49 days (Vos & van Driel-Grootenhuis, 1972; Vos & Van Genderen, 1973). In contrast, no effects were detected when dinitrochlorobenzene was used as the skin sensitizer in female Swiss-Webster mice fed Aroclor 1254 at 10, 100, or 250 ppm [1.17, 116, 292 mg/kg bw per week] for 12 weeks (Talcott & Koller, 1983). Similarly, White New Zealand male rabbits fed Aroclor 1254 at 170 ppm [6.54 mg/kg bw per day] for 56 days did not show any effects on skin reactivity to tuberculin sensitization (Street & Sharma, 1975).

Studies on the mitogen-induced proliferative activity of splenic mononuclear leukocytes and the mixed lymphocyte response, both in-vitro correlates of cellular immune responses, also gave conflicting results and suggested that PCBs may affect a specific subpopulation of T lymphocytes. A few studies reported that phytohaemagglutinin-induced leukocyte blastogenic activity was increased upon exposure to Aroclors, while no effect was noted when concanavalin A, *S. typhimurium*, or pokeweed mitogens were used (Bonnyns & Bastomsky, 1976; Wierda *et al.*, 1981; Smialowicz *et al.*, 1989). The mixed lymphocyte response was not affected by treatment with the less chlorinated Aroclor 1242 (Carter & Clancy, 1980; reviewed by Silkworth & Loose, 1981).

Nakanishi *et al.* (1995) treated female Sprague-Dawley rats (age, 8 weeks) intraperitoneally with 5 mg of Kanechlor 400 in 2 mL of corn oil, and effects on the immune system were examined at termination of the study 4 weeks later. The percentage of T lymphocytes, and T-helper and T-suppressor cells, was significantly decreased in the treated groups compared with the controls. In contrast, the percentage of T lymphocytes in the bronchoalveolar lavage fluid was not significantly increased after treatment with Kanechlor 400. The percentage of T-suppressor cells increased significantly, while the percentage of T-helper cells was not affected by treatment. Release of O_2^- by alveolar macrophages, stimulated with either wheat germ lectin or phorbol myristate acetate, increased significantly compared with the controls (Martin *et al.*, 1981). In addition, there was mild inflammation of the alveoli after administration of PCBs. In support of this observation, Kikuchi *et al.* (1971) reported that lung autopsies for two Yusho patients showed the presence of pulmonary haemorrhage and pulmonary oedema. [It is conceivable that failure to remove O_2^- produced by macrophages might be responsible for the observed pathogenesis of interstitial changes of the lung after treatment with PCBs].

(iv) Effects on innate (non-specific) immunity

The cellular components of innate immunity, including phagocytic cells (neutrophils, macrophages) and NK cells, are targets of PCB-induced immunotoxicity. Functional impairment of these cells is characterized by reduced phagocytic activity and consequently diminished ability to eliminate pathogenic infections in PCB-exposed experimental animals, as well as compromised immunosurveillance mechanisms.

Male ICR mice fed diets containing Kanechlor 500 at 400, 200, or 100 µg per gram feed showed increased susceptibility to herpes simplex virus compared with control mice (Imanishi *et al.*, 1980). Likewise, Koller (1977) demonstrated that Balb/c male mice fed diets containing Aroclor 1242 at 375 ppm for 6 months showed a significant increase in susceptibility to Moloney leukaemia virus; this effect was not seen with Aroclor 1221. In Balb/c male mice given feed containing Aroclor 1242 at 167 ppm for 6 weeks, there was significantly increased susceptibility to *S. typhosa* endotoxin and to malaria parasite *Plasmodium berghei* (Loose *et al.*, 1979). Reduced clearance of *Listeria monocytogenes* was observed in adult and neonate male and female ICR mice given Aroclor 1254 at 75 mg/kg bw per day by gavage for 14 days (Smith *et al.*, 1978). Thomas & Hinsdill (1980) reported increased sensitivity to endotoxin challenge in outbred, female albino mice fed Aroclor 1248 at 100 ppm, but no effect on resistance to *S. typhimurium* in mice fed Aroclor 1248 at 1000 ppm.

NK-cell activity was reported to be decreased in male Fischer 344 rats exposed daily to Aroclor 1254 at 10 or 25 mg/kg bw by gastric intubation for up to 15 weeks (Smialowicz *et al.*, 1989), and in male Sprague-Dawley rats fed Aroclor 1254 at 50 or 500 ppm for 10 weeks (Talcott *et al.*, 1985; Exon *et al.*, 1985).

Paradoxically, despite the evidence that PCB-induced immunosuppression impairs immune surveillance, Aroclor 1254 protected mice and rats against certain kinds of experimentally induced tumours, such as Ehrlich's tumour ascites (Keck, 1981) and primary Walker 256 tumour (Kerkvliet & Kimeldorf, 1977).

(e) Fish and marine mammals

As top predators, marine mammals and large fish bioaccumulate PCBs at high concentrations in fat. Several studies have reported on the immunotoxic effects of PCBs on fish and marine mammals in contaminated environments (Mahy *et al.*, 1988; Osterhaus & Vedder, 1988; Cleland *et al.*, 1989; Dietz *et al.*, 1989; Visser *et al.*, 1993; De Swart *et al.*, 1994; Ross *et al.*, 1995, 1996; Hammond *et al.*, 2005; Iwanowicz *et al.*, 2009; Frouin *et al.*, 2010; Duffy-Whritenour *et al.*, 2010).

4.3.5 Effects on inflammatory response

Several in-vivo and in-vitro studies have investigated the role of PCBs in the development of inflammatory responses, and are reviewed in the following section. Pertinent to this review are the following questions: (i) is the observed inflammation in PCB-treated animals directly related to PCB exposure, or is it a secondary development following PCB-induced toxicity in target organs; and (ii) does inflammation play an active role in the development of cancer after PCB exposure?

(a) Humans

No studies defining an association between exposure to PCBs and the development of inflammation in relation to cancer in humans were available to the Working Group.

(b) Experimental animals in vivo

(i) Commercial PCB mixtures

Tryphonas *et al.* (1984) reported significant changes indicative of an ongoing inflammatory response in the liver of cynomolgus monkeys *(Macaca fascicularis)* treated with Aroclor 1254 or Aroclor 1248. These changes included "ground glass" appearance of the cytoplasm and pyknosis of the nuclei with or without neutrophil infiltration, eosinophilic necrosis of single or clusters of hepatocytes often with neutrophilic infiltration or collapse of the connective tissue framework, and moderate, diffuse sinusoidal fibrosis and hypercellularity, and were associated with PCB-induced necrosis of the liver.

Interstitial inflammation of the liver was also observed in cynomolgus monkeys fed with

P-KC-400 (Kanechlor 400 from which PCDFs had been removed, largely containing tri- and tetrachlorobiphenyls), or PY-PCB (a PCB mixture with constituents similar to those ingested by Yusho patients, and largely containing penta- and hexachlorobiphenyls and no PCDF) at 5 mg per day, for 20 weeks (Hori *et al.*, 1982).

(ii) PCB congeners

Inflammatory responses, presumably secondary to PCB-induced toxic effects, have been reported in long-term studies of carcinogenicity in rats treated with PCB-126 (NTP, 2006a), PCB-153 (NTP, 2006b), PCB-126 + PCB-153 (NTP, 2006c, varying ratios study), PCB-126 + PCB-118 (NTP, 2006d), and PCB-118 (NTP, 2010). The incidence and severity of inflammation in the treated groups varied according to the congener administered. For PCB-118 and PCB-126, the incidence of inflammation and degree of severity were significantly increased in core groups receiving the three higher doses than in the controls, while for PCB-153, the incidence in the core groups was only slightly increased compared with the controls and was not dose-dependent. In addition to the core groups, inflammation, albeit of low incidence and intensity, was also observed in the control groups in the studies with PCB-118 and PCB-126, and in the uterus of rats in the PCB-153 control group, but not in the ovary of rats in the same group.

Sipka *et al.* (2008) investigated the potential for various PCB congeners to induce inflammation in mice. Mice were given a single gavage dose (150 µmol/kg bw) of PCB-77, PCB-104, or PCB-153. The levels of specific inflammatory mediators including intercellular adhesion molecules (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) mRNA and monocyte chemoattractant protein-1 mRNA (MCP-1) were determined in the liver, lung, and brain. All three PCB congeners activated inflammatory mediators, and the organs affected varied according to the congener used. PCB-77 and PCB-104 caused induction of all three inflammatory mediators in the liver and lungs, but not in the brain. In contrast, the effects of PCB-153 varied across mediators and were predominantly seen in the lung and brain. Concentrations of PCB-153 were higher in the lung and brain than in the liver, and PCB-153 was the only PCB to be detected in the brain (Sipka *et al.*, 2008). These observations suggested that the observed differences in target organ for the effects on inflammatory mediators were due to differences in PCB-congener accumulation in the organs affected.

In another study, a single dose of PCB-77 resulted in increased expression of VCAM-1 only in the wildtype (AhR-positive) mice, and not in mice lacking the AhR gene (Hennig *et al.*, 2002b).

Sipos *et al.* (2012) suggested that exposure to environmental toxicants including PCBs may cause vascular inflammation that facilitates the development of brain metastases. The crucial event in metastasis is adhesion of blood-borne tumour cells to the vascular endothelium, followed by transcapillary migration. In wild-type or ICAM-1-deficient mice injected with Lewis lung carcinoma cells via the carotid artery, oral pretreatment with PCB-118 enhanced development of brain metastases by inducing overexpression of ICAM-1 (also designated as CD54) and VCAM-1 in the brain endothelium (Sipos *et al.*, 2012).

(c) In-vitro studies

In-vitro studies by Narayanan *et al.* (1998) indicated that Aroclor 1242 and PCB-47 (a major constituent of Aroclor 1242) impaired the oxidative burst (respiratory burst) in human neutrophils by inhibiting the antioxidant enzyme superoxide dismutase, which converts O_2^- to H_2O_2. Pre-incubation of neutrophils with Aroclor 1242 or PCB-47 before stimulation with phorbol 12-myristate 13-acetate, elevated the respiratory burst, and resulted in a significant increase in intracellular O_2^- production and a significant

decrease in H_2O_2 compared with that in unexposed but agonist-stimulated neutrophils.

Additional in-vitro studies indicated that non-coplanar PCBs stimulate neutrophil production of superoxide anions (O_2^-) by a mechanism that is structure-specific and dependent on the chlorine substitution pattern of the biphenyl rings. On the contrary, coplanar congeners with high affinity for AhR do not activate neutrophils to produce superoxide anions and may inhibit this response (Brown *et al.*, 1998). In these studies, neutrophils were isolated from male Sprague-Dawley rats and exposed to specific PCB congeners at 0 (vehicle), 10, or 50 µM for 30 minutes at 37 °C, before stimulation with phorbol 12-myristate 13-acetate at 0 or 20 ng/mL. PCB-4, PCB-8, or PCB-11 (50 µM) stimulated neutrophils to produce O_2^-. Incubation of neutrophils with PCB-15, PCB-126, PCB-127, or PCB-128 did not result in generation of O_2^-. Of the various congeners tested, PCB-8 elicited the highest production of superoxide anions.

Exposure to PCB-4, PCB-8, PCB-11, or PCB-128 before addition of phorbol myristate acetate caused a significant increase in the amount of O_2^- produced that was greater than that seen with either compound alone. Phorbol myristate acetate-stimulated production of O_2^- was unaffected by prior exposure to PCB-15, PCB-126, or PCB-127. In separate experiments, PCB-126 inhibited the amount of O_2^- produced in response to activation with either PCB-4 or PCB-11. From these results it appeared that non-coplanar congeners are capable of stimulating neutrophil production of O_2^-. Coplanar congeners with a high affinity for AhR do not activate neutrophils to produce O_2^- and may inhibit this response.

Kwon *et al.* (2002) investigated the effects of PCB-153 on the expression of cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α in a human leukaemic mast cell line. The expression of TNF-α and IL-1β mRNA was not dependent on PCB-153, while the expression of COX-2 and IL-6 mRNA was highly induced by PCB-153. Pre-treatment with pyrrolidine dithiocarbamate, an NF-κB-pathway inhibitor, suppressed induction of COX-2, TNF-α and IL-1β, and reduced the induction of IL-6 mRNA by PCB-153.

The effects of PCBs on the activation of human granulocytes were investigated by Voie *et al.* (1998). Respiratory burst activity was measured as luminol-amplified chemoluminescence in human granulocytes. *Ortho*-substituted PCB congeners (PCB-47 and PCB-4) stimulated chemoluminescence in a concentration-dependent manner (ED_{50}, approximately 10 µM), while *meta*- and *para*-substituted congeners had no significant effect. Furthermore, using several enzyme-specific inhibitors, it was shown that PCB-activated chemiluminescence was dependent on Ca^{++}-dependent phospholipase D or phospholipase C, phosphatidylinositol 3-kinase, and protein kinase C activation before activation of the NADPH oxidase.

In an early experiment, porcine pulmonary artery-derived endothelial cells were incubated for up to 24 hours with PCB-77, PCB-114, or PCB-153, which were selected for their varying binding avidities to AhR and different capacities to induce CYP (Toborek *et al.*, 1995). PCB-77 and PCB-114 significantly disrupted endothelial barrier function in a dose-dependent manner by allowing an increase in albumin transfer across endothelial monolayers. PCB-77 and PCB-114 also enhanced oxidative stress (increasing levels of 2,7-dichlorofluorescein fluorescence, lipid hydroperoxides, and intracellular calcium) and caused increased activity and level of CYP 1A, and decreased levels of vitamin E in the culture medium. In contrast, incubation of endothelial cells with the non-dioxin-like PCB-153 did not have any effect on cellular oxidation, intracellular calcium levels, or on endothelial barrier function.

Additional in-vitro experiments (Hennig *et al.*, 1999; 2002a, 2002b) further suggested

that PCBs are atherogenic, exerting their effect by disrupting normal cellular functions of the vascular endothelium, and confirmed that oxidative stress and activation of the CYP1A subfamily may play a role in the events that lead to atherogenicity.

Treatment of porcine endothelial cells with the DL-PCBs PCB-77, PCB-126, or PCB-169 resulted in increases in expression of the *CYP1A1* gene, oxidative stress, and the DNA-binding activity of NF-κB in a concentration-dependent manner. PCB-126 elicited a maximal response at the lowest concentration (0.5 μM) tested. In addition, all three coplanar PCBs increased endothelial production of IL-6. The expression of adhesion molecule VCAM-1 by endothelial cells was highest at 3.4 μM PCB-77 or PCB-169 (Hennig *et al.*, 2002b).

When human umbilical vein endothelial cells (HUVEC) were treated with PCB-104, a non-coplanar congener, PCB-104 increased the oxidative stress and markedly upregulated the expression of monocyte chemoattractant protein-1 (MCP-1), and the adhesion molecules E-selectin, and ICAM-1, at both the mRNA and protein levels, in a time and concentration-dependent manner. Furthermore, PCB-104 stimulated the adhesion of THP-1 cells (a human acute monocytic leukaemia cell line) to endothelial cell monolayers (Choi *et al.*, 2003).

4.3.6 Quantitative structure–activity relationships (QSAR)

Based on their structure–activity characteristics, PCB congeners are generally grouped as dioxin-like and non-dioxin-like (see Section 1.1.1):

- DL-PCBs are *meta*-/*para*-chloro-substituted PCBs and include PCB-77, PCB-126, PCB-169 and their mono-*ortho*-chlorinated derivatives. These congeners can adopt a coplanar structure and display avid binding to AhR (avidity to AhR diminishes with *ortho*-chloro-substitution). AhR activation leads to a multitude of biological and toxic manifestations, referred to as "dioxin-like activity".
- NDL-PCBs are *ortho*/*para*-substituted PCBs. *Ortho*/*para*-substitution (at least two chlorines in *ortho* positions) is associated with the capacity to induce CAR/PXR-dependent gene expression (e.g. CYP2B, CYP3A isoenzymes). CAR agonists have substitutions in *ortho*, *para* with or without *meta* substitution, while PXR agonists and ryanodine agonists have multiple *ortho* positions substituted with chlorines.
- Some PCB congeners do not elicit activation of AhR, CAR, or PXR.

PCB congeners can also be grouped as lower- and higher-chlorinated congeners. The number of chlorine substituents is linked to persistency and bioaccumulation in animals and humans; less chlorinated congeners are typically volatile and metabolically active, and may produce ROS and genotoxic insults (see Section 4.2).

Additionally, a specific configuration may show activity in a specific bioassay, e.g. for endocrine effects (especially modulation of steroid and thyroid nuclear receptors), neurotoxic activities (release of a neurotransmitter, calcium homeostasis), and/or events associated with tumour promotion (e.g. inhibition of GJIC) (see Section 4.3.2).

The TEQ concept used for risk assessement of PCBs is based on AhR-mediated toxicity of DL-PCBs (see Section 4.3.1). In contrast, the toxicity profiles of NDL-PCBs are insufficiently characterized.

Defining key structural toxicity determinants of individual congeners modulating CAR-, PXR-, androgen receptor-, estrogen receptor-, and other receptor-dependent gene expression is not easy; with the exception of AhR, androgen receptor, and estrogen receptor, there were no systematic studies comparing a large series of PCB congeners in a receptor-based bioassay.

Only a few specific QSAR studies addressing carcinogenicity of PCBs have been published. Ruiz *et al.* (2008) attempted to predict mutagenicity and carcinogenicity of all 209 PCB congeners and some oxidative metabolites using experimental data on DNA-adduct formation, on GJIC-inhibition potency, and National Toxicology Program (NTP) rodent carcinogenicity bioassays. Interestingly, a positive mutagenicity activity was predicted for the less chlorinated PCBs and their hydroxy- and benzoquinone metabolites. Carcinogenicity of many di- to hexachlorinated PCBs was predicted by the QSAR based on NTP carcinogenicity studies in mice, while no carcinogenicity was predicted for tested congeners in the analysis for rats. [A significant drawback was that carcinogenicity predictions were not applicable for the highly abundant, higher-chlorinated congeners PCB-153, PCB-170 and PCB-180 (predicted values were outside the optimum prediction space). Therefore QSAR analyses of carcinogenicity of PCB congeners were inadequate, especially when regarding possible extrapolation to hazards in humans.]

An alternative and more complex approach was reported recently by Stenberg *et al.* (2011). Multivariate toxicity profiles and QSAR modelling of NDL-PCBs were used, based on a variety of molecular descriptors. The toxicity profiles of 24 selected PCBs were identified by in-vitro screening; the different mechanisms of action, which were mostly related to endocrine disruption and neurotoxicity, also included tumour promotion. NDL-PCBs were highly purified, to exclude any contaminating dioxin-like compounds before testing (Hamers *et al.*, 2011). QSAR analysis included also several parameters relevant to carcinogenicity, such as ROS production and inhibition of GJIC. Principal component analysis was used to derive general toxicity profiles from experimental in-vitro data, and individual QSAR models were calculated for each in-vitro response using a set of 67 chemical descriptors. It was shown that PCBs could be divided into at least three major clusters; the DL-PCBs, and two separate NDL-PCB clusters with similar toxicity profiles. The first NDL-PCB cluster included mainly less-chlorinated, *ortho*-substituted congeners with generally higher biological activities (e.g. PCB-28, PCB-95, PCB-101, PCB-136); this subset of congeners was also the most active in the study of GJIC inhibition. The second cluster of NDL-PCBs included congeners with a narrow effective concentration and lower biological activities, with the exception of three assays related to endocrine activity (e.g. PCB-118, PCB-138, PCB-153, PCB-170, PCB-180) (Stenberg *et al.*, 2011).

QSAR approaches might become a useful tool for evaluation and prediction of toxicity of PCBs related to carcinogenesis; however, currently their use is hampered by the lack of data on specific mechanisms of action for larger congener sets.

4.4 Organ toxicity relevant to carcinogenicity

The reader is referred to Section 3.1.2 and Table 3.1 for study design and additional results of the experiments described below.

4.4.1 Hepatic preneoplastic lesions

(a) Promotion of preneoplastic lesions

(i) Commercial PCB mixtures

PCB mixtures, including Aroclor 1254, Clophen A 30, Clophen A 50, and Phenoclor DP6, have shown promoting activity in liver carcinogenesis (Glauert *et al.*, 2001). Several initiating agents were used, including diethylnitrosamine (DEN), aflatoxin B_1, and benzo[*a*]pyrene. The following markers of altered hepatic foci were used in these studies: gamma-glutamyl transferase (GGT), ATPase, and glycogen. The promoting activity of PCBs was observed in males and females. In one study, the promoting activity

of Clophen A 50 was much higher in female rats than in males (Deml & Oesterle, 1982); a similar observation was made for phenobarbital (Xu *et al.*, 1990). In mice, males are more susceptible than females to hepatocarcinogenesis; higher production of IL-6 by Kupffer cells in males may be responsible for this sex-specific difference (Naugler *et al.*, 2007). In a dose–response study with Clophen A 50, a threshold dose (1 mg/kg bw, three times per week, for 11 weeks) was identified (Deml & Oesterle, 1987).

(ii) Individual congeners

Many studies have examined the ability of individual PCB congeners to promote altered hepatic foci in rat liver (Glauert *et al.*, 2001). Most of the studies used DEN as the initiating agent, whether as a single necrogenic dose, as a low dose in conjunction with partial hepatectomy, as a low dose in newborn animals, or in the drinking-water for 10–12 days. The following markers of altered hepatic foci were used in these studies: GGT, GSTπ, ATPase, and/or glucose-6-phosphatase. PCB congeners that had promoting activity included non-*ortho* PCBs (PCB-77 and PCB-126), which activated AhR; di-*ortho*-substituted PCBs (PCB-47, PCB-49, and PCB-153), which activated CAR; and mono-*ortho*-substituted PCBs (PCB-105, PCB-114, PCB-118, and PCB-156), which activated both receptors. Non-*ortho*-PCBs were the most efficacious (Glauert *et al.*, 2001). PCBs that did not induce (PCB-3 and PCB-15) or that weakly induced (PCB-28 and PCB-101) either receptor had poor promoting activity (Oesterle & Deml, 1981; Deml *et al.*, 1985; Buchmann *et al.*, 1991; Kunz *et al.*, 2006). [These differences could be due to pharmacokinetics as well as pharmacodynamics.]

(iii) Combinations of individual congeners

Several studies have investigated the effects of administering combinations of two or more PCB congeners. Most of these studies found that the co-administration of non-*ortho* and di-*ortho* PCBs produced less than additive effects, while administration of two non-*ortho* PCBs produced additive effects. These studies used DEN as the initiating agent, either as a low dose in combination with partial hepatectomy, or as a hepatotoxic dose.

In the earliest study, Sargent *et al.* (1991) examined the separate and combined effects of dietary administration of (di-*ortho*) PCB-52 at 10 ppm, and (non-*ortho*) PCB-77 at 0.1 ppm for 1 year in rats. When administered separately, PCB-77 did not increase the number or volume of altered hepatic foci, but PCB-52 increased the volume fraction but not the number of altered hepatic foci. Coadministration of PCB-52 and PCB-77, however, increased both the number and volume fraction of altered hepatic foci in a more than additive manner. In a study examining the interactive effects of a non-*ortho*-substituted PCB (PCB-126), a mono-*ortho*-substituted PCB (PCB-105), and a di-*ortho*-substituted PCB (PCB-153), no more than additive effects were observed. An additive effect was observed with PCB-105 + PCB-153, while less than additive effects were observed for PCB-126 + PCB-153, and for PCB-126 + PCB-105 (Haag-Grönlund *et al.*, 1998). In another study, PCB-77 and PCB-153 were administered every 2 weeks separately at 300 µmol/kg bw, or in combination at 150 µmol/kg bw (total PCB dose, 300 µmol/kg per injection) for four injections (Berberian *et al.*, 1995). Numbers and volume of foci induced by PCB-77 were decreased by the coadministration of PCB-153. In a study using a similar experimental design, rats were injected four times with PCB-77 or PCB-153 (100 or 300 µmol/kg bw), or PCB-77 + PCB-153 (100 µmol/kg bw each) biweekly. Both PCB-77 and PCB-153 separately increased the number and volume of GSTP-positive foci, but coadministration of PCB-153 inhibited the number and volume of foci induced by PCB-77 (Tharappel *et al.*, 2002). When PCB-126 (non-*ortho*) and PCB-153 (di-*ortho*) were coadministered using 14 combinations of doses, a less

than additive effect was observed (Dean *et al.*, 2002). Finally, the tumour-promoting activity of a polyhalogenated aromatic hydrocarbon mixture (TCDD; 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin; 2,3,4,7,8-pentachlorodibenzofuran; PCB-126; PCB-118; and PCB-156) with or without PCB-153 (di-*ortho*) was compared with that of TCDD alone, the mixture and TCDD having the same total TEF (van der Plas *et al.*, 1999). The mixture produced a lower mean volume of foci and volume fraction of foci in the liver than did TCDD alone. The addition of PCB-153 slightly increased the mean volume of foci and volume fraction of foci in the liver, but still not above that produced by TCDD alone. TCDD and PCB-126 (non-*ortho*) were found to have an additive effect in another study (Hemming *et al.*, 1995).

(b) Initiation of preneoplastic lesions

Studies examining the effect of PCBs as initiating agents fell into two categories: those that examined the effect of PCB treatment with no subsequent chemical treatment, and those in which PCB treatment was followed with protocols designed to shorten the latency period and increase the number and size of lesions, such as the Solt-Farber selection protocol (Solt *et al.*, 1977; Tsuda *et al.*, 1980; Semple-Roberts *et al.*, 1987). Groups of animals treated with PCBs only were often control groups in initiation–promotion studies, e.g. PCB-only groups being used to compare initiator + PCB groups.

Several studies have observed a small increase in the number of altered hepatic foci after treatment with PCBs only. These PCBs included Clophen A 50, PCB-49, PCB-77, and PCB-114 (reviewed in Glauert *et al.*, 2001). There are two possible explanations for this phenomenon: first, these PCBs have initiating activity; or second, these PCBs are very efficient at promoting cells that have initiated spontaneously (e.g. from errors in DNA replication, exposure to background chemicals or radiation, etc.). Other studies, however, have observed that certain PCBs, including Aroclor 1254, Clophen A 50, PCB-52, PCB-77, and PCB-153, do not produce any increase in the number of altered hepatic foci after treatment with the PCB congener only (reviewed in Glauert *et al.*, 2001). [Possible reasons for obtaining different results for the same PCBs included use of different doses, use of different proliferative stimuli, and different latency periods.]

Three studies have used PCBs as initiating agents in the Solt-Farber protocol to determine whether altered hepatic foci would develop. This protocol involves treatment with an initiating agent (either known or to be tested) in conjunction with a proliferative stimulus. After a recovery period (usually 2 weeks), rats are treated with 2-acetylaminofluorene (2-AAF; to inhibit cell proliferation), given either in the diet or by gavage, for 2 weeks, with a proliferative stimulus (usually an oral dose of carbon tetrachloride or partial hepatectomy) after the first week.

Hayes *et al.* (1985) assessed Aroclor 1254, a reconstituted human breast milk mixture of PCB congeners, PCB-47, PCB-52, and PCB-153, and found that none of them had initiating activity. Espandiari *et al.* (2003) examined less chlorinated PCBs, and observed that some (PCB-3, PCB-15, PCB-52, and PCB-77) increased the number of GGT-positive foci, while others did not (PCB-12 and PCB-38). A subsequent study showed that the PCB-3 metabolites 4-OH-PCB-3 and the *ortho* 3,4-quinone of PCB-3 acted as the proximate and ultimate carcinogens (Espandiari *et al.*, 2004). [Negative results obtained after the administration of PCBs could indicate lack of initiating activity, likely due to low metabolic activation, or could be caused by alteration of other components of the protocol, such as acetylaminofluorene metabolism and effects.]

4.4.2 Liver

Liver toxicity is commonly observed in long-term studies in rats and mice exposed to PCBs, with dose- and duration-dependent increases in the incidence, severity, and breadth of spectrum of lesions observed (Kimbrough & Linder 1974; Mayes *et al.*, 1998; NTP, 2006a, c, d, 2010).

For PCB-126, PCB-118, and binary mixtures of PCB-126 with PCB-153 or PCB-118, hepatic toxicity increased with increasing dose and duration of exposure, and was characterized by increases in the incidence and severity of hepatocyte hypertrophy (most likely due to alterations in PCB-induced CYP expression), diffuse fatty changes, multinucleated hepatocytes, pigmentation (likely due to haemosiderin accumulation), inflammation, altered hepatic foci, necrosis, oval cell hyperplasia, cholangiofibrosis, bile-duct hyperplasia, bile-duct cysts, and nodular hyperplasia (NTP, 2006a, c, d, 2010).

With PCB-153, hepatocyte hypertrophy was seen after 14, 31, and 53 weeks in female rats treated with doses of up to 3 mg/kg bw by gavage; at 2 years, there were also increases in the incidence of fatty change, bile-duct hyperplasia, oval-cell hyperplasia and pigmentation (NTP, 2006b).

While none of these hepatic responses are specifically preneoplastic, cholangiofibrosis and cholangiocarcinoma represent different diagnoses along the same continuum of pathogenesis. Cholangiofibrosis was seen in the above-mentioned NTP studies of female rats treated with specific PCB congeners by gavage, in female rats fed with Aroclor 1260 (Kimbrough *et al.*, 1975), and in female rats treated with other dioxin-like compounds by gavage (NTP, 2006e, f, g). In general, the higher the dose and duration of exposure, the higher the incidence, severity, and breadth of spectrum of responses observed. The observations of biliary and hepatocellular lesions are characteristic of an initial insult and the response of the liver to repair the injury and regenerate, leading to a hepatic stem-cell response and a bifurcating lineage of subsequent pathologies of both bile-duct cells and hepatocytes.

4.4.3 Lung

In the long-term NTP studies in female Harlan Sprague-Dawley rats treated with PCB-126, PCB-118, PCB-118 + 126 and PCB-126 + 153 by gavage, there were clear increases in the incidence of cystic keratinizing epithelium of the lung and of squamous cell carcinoma (NTP, 2006a, c, d, 2010). The two common effects seen in PCB-treated rats were an increased incidence of alveolar epithelial bronchiolar metaplasia and of squamous metaplasia of the lung (reviewed in Sells *et al.*, 2007). Squamous metaplasia was characterized by the transition of alveolar epithelial cells to squamous metaplastic cells with distortion of the normal architecture. Keratin formation was evident and inflammation was sometimes observed. The more expansive lesions formed keratinizing cysts, which consisted of a cystic structure with a thin uniform wall composed of mature squamous cells that contained various amounts of keratin. The term "cystic keratinizing epithelioma" was used for a benign neoplasm in this family of lesions, and "squamous cell carcinoma" was used as a diagnosis for the malignant form of the lesion (Sells *et al.*, 2007). Alveolar epithelial bronchiolar metaplasia was characterized by metaplasia of alveolar epithelium to respiratory type primarily at the junction of the terminal bronchioles and along alveolar ducts. Alveolar epithelial bronchiolar metaplasia did not appear to be associated with progression to neoplasia, but may have been characteristic of increased metabolic activity in the metaplastic area (Brix *et al.*, 2004).

No pulmonary toxicity was observed in a long-term NTP study with PCB-153 in female rats (NTP, 2006b). Pulmonary toxicity was not reported in long-term bioassays with Aroclors 1016, 1242, 1254, and 1260 in CD Sprague-Dawley

rats (Mayes *et al.*, 1998). [Differences between the studies included strain of rat used (Harlan Sprague-Dawley versus Charles River Sprague-Dawley), route of exposure (feed for Aroclors versus gavage for the PCB congeners), and use of complex mixtures (Aroclors) versus individual or binary mixtures of single PCB congeners.]

4.4.4 Thyroid

In long-term NTP studies of female Sprague-Dawley rats treated with PCB-126, PCB-118, PCB-126 + 118, and PCB-126 + 153 by gavage, there were increased incidences of follicular cell hypertrophy of the thyroid in the exposed groups at 14, 31, 53 weeks, and 2 years (NTP, 2006a, c, d, 2010; Yoshizawa *et al.*, 2010). Increased incidence of follicular cell hypertrophy was also seen with PCB-153 only at 53 weeks and 2 years (NTP, 2006b).

The observation of thyroid follicular cell hypertrophy in treated rats was attributed to alterations in the expression of UDP-GT in the liver, leading to a decrease in circulating T4, disruption of thyroid-hormone homeostasis, and compensatory hypertrophy (Hill *et al.*, 1989). [The Working Group noted that other mechanisms may be operational.] A persistent increase in the incidence of follicular cell hypertrophy has often been linked to increased incidences of follicular cell tumours of the thyroid in studies in experimental animals (see Section 3). No neoplasms were observed in treated females. Increased incidence of thyroid follicular cell tumours was seen in male CD SD rats exposed to Aroclors 1242, 1254, or 1260, although without significant increase in the incidence of thyroid follicular cell hypertrophy (Mayes *et al.*, 1998). The morphological appearance of the thyroid tumours was characteristic of those developed as a secondary response to chronic overstimulation of TSH. [This phenomenon is more common in males than females rats due to higher circulating levels of TSH in males.]

4.4.5 Adrenal gland

In the long-term NTP study in female Harlan Sprague-Dawley rats treated with PCB-126 by gavage, increased incidences of adrenal atrophy and cytoplasmic vacuolization were observed in those groups in which elevated incidences of adrenal adenoma were seen (NTP, 2006a). In long-term NTP studies in female rats treated with PCB-118, increases in the incidence of adrenal atrophy and cytoplasmic vacuolization, but not adrenal adenoma, were observed (NTP, 2010). Treatment with PCB-153 or Aroclors had no effect on the adrenal gland in long-term studies in female rats (Mayes *et al.*, 1998; NTP, 2006b).

4.4.6 Pancreas

A common occurrence in long-term studies with PCBs with dioxin-like activity (PCB-126, PCB-118, PCB-126 + PCB-118, and PCB-126 + PCB-153) in female rats (males were not studied) was toxicity in the pancreas (NTP, 2006a, c, d, 2010). In the NTP studies with PCB-126 and PCB-118, pancreatic acinar cytoplasmic vacuolization, atrophy, and chronic active inflammation were observed. No effect on the pancreas was seen in female rats exposed to PCB-153 at doses of up to 3 mg/kg bw per day for 2 years (NTP, 2006b). Increased incidence of acinar adenoma was observed in a long-term NTP study of PCB-126/153 in female rats, and sporadic incidences of acinar adenoma were observed in a long-term NTP study of PCB-118 in female rats, although it was uncertain whether this was a treatment-related effect (NTP, 2006c, 2010).

4.4.7 Female reproductive system

In the long-term NTP study of PCB-118 and PCB-153 in female Harlan Sprague-Dawley rats, there was no increase in the incidence of cystic endometrial hyperplasia of the uterus and squamous metaplasia of the uterus; the incidences of squamous metaplasia and cystic endometrial

hyperplasia in the core study groups were significantly less than the incidence in the vehicle-control group. In the PCB-118 stop-exposure group, in which exposure (to 4600 µg/kg bw) was for only 30 weeks followed by vehicle only (corn oil) for up to 2 years, the incidences of these two lesions were significantly increased compared with those in the core-study group exposed continually at 4600 µg/kg bw per day (NTP, 2006b, 2010). Accordingly, there was a significant increase in the incidence of uterine carcinoma in the stop-exposure group in which exposure was for only 30 weeks followed by vehicle only (corn oil) for up to 2 years, but not in the long-term exposure group (see Section 3.1.1). While the mechanism was not known, it was speculated that exposure to PCB-118 for the first 30 weeks led to the early development of responsive uterine carcinoma, and that the subsequent cessation of exposure reestablished a normal estrogenic milieu that promoted the development of these uterine neoplasms, which would otherwise have been suppressed if exposure had been continued for the full 2 years (Yoshizawa *et al.*, 2009).

In the 2-year NTP study with PCB-153 in female Harlan Sprague-Dawley rats, there was a significant increase in the incidence of chronic active inflammation of the ovary; however, there was no increase in the incidence of ovarian tumours (NTP, 2006b).

4.4.8 Skin

Chloracne and other dermal alterations are well known effects of long-term exposure to PCBs and related compounds (ATSDR, 2000). These effects have been reported in workers exposed occupationally to PCBs, and also in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs (Yusho and Yucheng), and in rhesus monkeys fed a diet containing Aroclor 1248. Chloracne is probably caused by interference of PCBs with the metabolism of vitamin A in the skin, resulting in disturbances of the epithelial tissues of the pilo-sebaceous duct (Coenraads *et al.*, 1994).

(a) Human exposure

(i) Occupational exposure

Chloracne is the most easily recognized effect of exposure to PCBs and structurally related chlorinated organic chemicals (Rice & Cohen, 1996). Chloracne first develops on the face, under the eyes and behind the ears, but severe chloracne can cover the entire body. Histologically, the lesions consist of keratinous cysts caused by squamous metaplasia of sebaceous glands. The acute stage is followed by vermiculite skin atrophy. Mild to moderate chloracne was observed in 7 out of 14 workers exposed to Aroclors (formulation not specified) at 0.1 mg/m^3 for an average duration of 14.3 months (Meigs *et al.*, 1954). [Because PCBs were used as a heat-exchange material, it is possible that these workers were exposed to pyrolysis products.] Three cases of chloracne occurred among autoclave operators (number not specified) exposed to Aroclor 1254 at 5.2–6.8 mg/m^3 for 4–7 months (Bertazzi *et al.*, 1987). [The presence of pyrolysis products may have been a confounding factor.] In 1977, four more cases of chloracne were diagnosed among 67 workers from the same plant who were engaged in impregnating capacitors with Pyralene 3010 (0.048–0.275 mg/m^3) and had skin contact confirmed as a major exposure route. An increased incidence of non-adolescent acneiform eruptions was reported in workers exposed to various Aroclors at mean concentrations of 0.007–11 mg/m^3 for > 5 years; 40% of the workers had been exposed for > 20 years (Fischbein *et al.* 1979, 1982). Maroni *et al.* (1981a, b) reported ten cases of acne and/or folliculitis and five cases of dermatitis among 80 capacitor-manufacturing workers in Italy. All the workers with chloracne were employed in jobs with high exposure. Their blood PCB concentrations ranged from 300 to 500 µg/L. No definite association was found

between chloracne and blood PCB concentrations. Other dermal effects reported in workers included skin rashes, pigmentation, disturbances of skin and nails, erythema and thickening of the skin, and burning sensations (Ouw *et al.*, 1976; Fischbein *et al.*, 1979, 1982; Smith *et al.*, 1982). In these studies, the workers were exposed to various Aroclors at concentrations as low as 0.003 mg/m^3 for > 5 years. In those studies that looked at PCB profile of exposure, statistically significant associations between dermatological effects and plasma concentrations of more highly chlorinated PCB congeners were reported (Fischbein *et al.*, 1979, 1982; Smith *et al.*, 1982), while no relationships were found between the incidence of skin rash or dermatitis, and plasma concentrations of less chlorinated PCBs (Smith *et al.*, 1982).

(ii) Accidental exposure

Skin effects were widely reported among victims of the Yusho and Yucheng poisoning episodes (Lü & Wu, 1985; Kuratsune, 1989; Rogan, 1989; Guo *et al.*, 1999). However, these effects could not be attributed solely to exposure to PCBs, since the victims were also exposed to PCDFs and other chlorinated chemicals (ATSDR, 1994). Characteristic skin changes included marked enlargement, elevation and keratotic plugging of follicular orifices, comedo formation, acneform eruptions, hyperpigmentation, hyperkeratosis, and deformed nails. Dark-coloured pigmentation frequently occurred in the gingival and buccal mucosa, lips, and nails, and improved only gradually in most patients (Kuratsune *et al.*, 1971; Fu, 1984; Lü & Wu, 1985; Kuratsune, 1989; Rogan, 1989). At 14 years after the Yucheng incident, exposed men and women had a higher lifetime prevalence of chloracne, abnormal nails, hyperkeratosis, and gum pigmentation (Guo *et al.*, 1999). Skin lesions were commonly observed in children born to mothers exposed during the Yusho or Yucheng incidents (Gladen *et al.*, 1990).

(b) Experimental systems

(i) Animal studies in vivo

Female rhesus monkeys fed diets containing Aroclor 1248 at concentrations of 2.5 and 5.0 ppm developed facial oedema, swollen eyelids, erythema, loss of hair, and acne, within 2 months. After 6 months, the monkeys were bred with control males. In the seven offspring carried to term, and exposed for 4 months to PCBs via the lactating mother, focal areas of hyperpigmentation and acneiform lesions of the face developed within 2 months, and were accompanied by increased skin PCB concentrations (Allen & Norback, 1976).

Developing *Xenopus laevis* tadpoles were exposed to Aroclor 1254 at concentrations of 0 to 100 µg/mL from day 5 to day 9 after fertilization. Exposure at the higher concentrations (10, 50, and 100 µg/mL) caused statistically significant reductions in survival and body size, and resulted in histological abnormalities, including aberrant tail-tips, and aberrant myotomal and melanocyte morphologies; tadpoles treated with Aroclor 1254 were devoid of dendritic arborizations, resulting in decrease in total melanocyte area (Fisher *et al.*, 2003).

(ii) Human cells in vitro

Only two studies were available on the molecular effects of PCBs in human skin cells. Exposure of normal human melanocytes to TCDD resulted in activation of the AhR signalling pathway, AhR-dependent induction of tyrosinase, and consequently, elevated total melanin content. These effects were due to the induction of tyrosinase and tyrosinase-related protein 2-gene expression. Thus AhR is able to modulate melanogenesis by controlling the expression of melanogenic genes (Luecke *et al.*, 2010).

Exposure of human skin keratinocytes to a synthetic mixture of volatile PCBs, or the common airborne congeners PCB-28 or PCB-52

led to significant inhibition of telomerase activity and reduced telomere length. All PCBs decreased cell proliferation, and PCB-52 produced a small increase in the fraction of cells arrested in G0/G1 of the cell cycle. Changes in telomere length and telomerase activity are hallmarks of ageing and carcinogenesis; these effects suggested a potential mechanism by which exposure to PCBs could lead to skin cancer (Senthilkumar *et al.*, 2011).

4.5 Susceptibility

4.5.1 Genetic polymorphisms

Single nucleotide polymorphisms in the genes for metabolizing enzymes or receptors can potentially affect expression or inducibility (if these polymorphisms were in the promoter region of the gene), and stability or function of the protein (if they were in the coding region). The individual response to carcinogens may be influenced by polymorphisms in genes for metabolizing enzymes, including xenobiotic- and steroid-metabolizing CYP, GST, catechol *O*-methyltransferase (COMT), and others (Singh *et al.*, 2008); receptors that control expression of metabolizing enzymes such as AhR (Ng *et al.*, 2010) and the AhR repressor (Hung *et al.*, 2013); and receptors that interact with endogenous molecules such as steroid hormones.

(a) Metabolizing genes

As discussed in Section 4.1.3, CYP plays an important role in PCB metabolism. Knowledge of the particular CYP isoform most likely to bind and/or metabolize a PCB congener is important in evaluating risk from exposure to this congener. Many human CYP isoforms exhibit pharmacogenetic polymorphisms, which can affect expression levels, catalytic activity per unit enzyme with particular substrates, or both parameters (Ingelman-Sundberg *et al.*, 2007). Variations in activity due to polymorphism could lead to inter-individual differences in the capacity to metabolize particular congeners. If metabolism of the congener produced genotoxic metabolites, such as arene oxides, quinones, or reactive oxygen species through the action of CYP, this could mean that greater amounts of these potential carcinogens would be formed in some individuals with increased metabolic activity. Alternatively, people with a lower metabolic activity for some PCBs could accumulate greater amounts of those PCBs, if continually exposed. Both scenarios could lead to increased risk of cancer, through several mechanisms.

(i) Cancer of the breast

Epidemiological studies have provided evidence for increased risk of cancer of the breast in women with a particular genetic polymorphism in the *CYP1A1* gene and high serum PCB concentrations (Moysich *et al.*, 1999; Laden *et al.*, 2002; Charlier *et al.*, 2004; Zhang *et al.*, 2004; Li *et al.*, 2005). In the variant form, *CYP1A1*2C*, also called the m2 variant, has valine substituted for isoleucine at position 462 near the *C* terminus of the protein (Persson *et al.*, 1997). This variant is found in 10–15% of the white population and in a larger proportion of African-Americans (reviewed in Brody *et al.*, 2007). Persson *et al.* (1997) reported that the activity per unit enzyme of this variant, measured in vitro, was similar to that of wildtype *CYP1A1*. Polymorphisms in AhR, or its repressor, that influence the expression of *CYP1A1* may be more important than *CYP1A1* genotype in determining the in-vivo activity of *CYP1A1* (Smart & Daly, 2000; Hung *et al.*, 2013).

Among postmenopausal patients with cancer of the breast in western New York state, USA, the incidence of cancer of the breast was higher in women with total PCB concentrations (73 congeners) of 3.73–19.04 ng/g of serum and the *CYP1A1*2C* polymorphism than in women with lower PCB concentrations or wildtype *CYP1A1* (Moysich *et al.*, 1999). In a study of Caucasian women in Connecticut, USA, in which serum

concentrations of PCB-74, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, and PCB-187 were measured, cancer of the breast was more prevalent in postmenopausal women with lipid-adjusted serum concentrations of 611–2600 ng/g and the *CYP1A1*2C* polymorphism than in controls (Zhang *et al.*, 2004). If the *CYP1A1* polymorphism was absent (homozygous wildtype alleles), there was no effect of serum PCB concentration on incidence of cancer of the breast. An epidemiological study of African-American and white women in North Carolina, USA, examined lipid-adjusted total plasma PCB concentrations, *CYP1A1* polymorphism, and risk of cancer of the breast (Li *et al.*, 2005). Although results were not conclusive due to small sample size, premenopausal white women with cancer of the breast were more likely to have total PCB concentration > 0.35 ng/mL serum and the *CYP1A1*2C* polymorphism than were controls, while there was no relationship between cancer of the breast in women with total PCB concentration < 0.35 ng/mL serum or lacking this polymorphism. In the African-American women, total PCB concentrations were somewhat higher (≥ 0.430 ng/mL), and the *CYP1A1*3* polymorphism was more prevalent in pre- and postmenopausal patients with cancer of the breast (Li *et al.*, 2005).

Another study found a non-significantly elevated risk of cancer of the breast among women with the CYP1A1-m1 variant and high serum PCB concentrations (McCready *et al.*, 2004).

(ii) Cancer of the testis

Data from 568 cases of testicular cancer and 698 controls enrolled in the United States Servicemen's Testicular Tumor Environmental and Endocrine Determinants Study were used to examine associations between testicular germ cell tumours (TGCT) and exposure to PCBs, as affected by polymorphisms in several hormone-metabolizing genes, i.e. *CYP17A1*, *CYP1A1*, *HSD17B1*, *HSD17B4* and androgen receptor. Among these, the polymorphism rs384346 in *HSD17B4* modified the association of TGCT risk with PCB-118 and PCB-138 concentrations. Among men who were homozygous for the major allele genotype, there was a statistically significant dose-dependent reduction in risk (P for trend, < 0.001) with higher exposure to PCB-118 and PCB-138. Men in the highest quartile of PCB-118 exposure had an almost 50% reduction in risk of TGCT (OR, 0.46, 95% CI, 0.31–0.70) compared with men in the lowest quartile; similar results were seen for PCB-138. For any minor allele of this *HSD17B4* polymorphism, there were no associations between PCB-118 and PCB-138 concentrations and risk of TGCT. No interactions between other PCB congeners of interest (PCB-153, PCB-156, PCB-163, PCB-170, PCB-180, and PCB-187) and enzyme polymorphism were observed (Chia *et al.*, 2010).

(b) Polymorphisms in other genes

Among highly exposed Yucheng patients, combined *CYP1A1-Msp1* mutant genotype and *GSTM1-null* genotype were associated with an increased risk of chloracne (OR, 2.8; 95% CI, 1.1–7.6). Among intermediately exposed individuals, the *GSTM1-null* genotype was associated with skin allergy (Tsai *et al.*, 2006).

Patients with non-Hodgkin lymphoma and PCB-118 concentrations in the highest quartile (> 12.85–202.13 µg/L plasma) were more likely to have a polymorphic variant of AhR (IVS + 4640 null; G/G genotype) than controls, although the effect was not strong and was also related to highest levels of oxychlordane and *trans*-nonachlor (Ng *et al.*, 2010).

Among women with cancer of the breast who carried a variant of the tumour-suppressor gene *TP53*, total PCB exposure in the highest quartile was associated with an increased risk of cancer of the breast, but this was not statistically significant (OR, 3.0; 95% CI, 0.66–13.62) (Høyer *et al.*, 2002).

4.5.2 Exposure in utero, postnatally, and of children

PCBs can pass through the placenta during embryonic development and accumulate in breast milk. In addition, compared with adults, children have a lower barrier to absorption through the skin, gastrointestinal tract and lungs, and lower levels of detoxifying enzymes (Lindström *et al.*, 1995). A combination of all these factors leads to a higher accumulation of PCBs in children.

(a) Toxicokinetics and distribution in tissues

(i) Children

Grandjean *et al.* (2008) studied the elimination kinetics of PCBs in two groups of children with elevated PCB concentrations due to breastfeeding. Children were followed from age 4.5 to 7.3 years (99 subjects) and 7 to 14 years (101 subjects). Subjects with exposures above the median and in the highest quartile showed half-lives of about 3–4 years for PCB-138; 4.5–5.5 years for PCB-105 and PCB-118; 6.5–7.5 years for PCBs 156, 170 and 187; and 7–9 years for PCBs 153 and 180. The longest half-lives correspond to elimination of the parent PCB solely with a daily fat excretion rate of 1–2 g, while shorter half-lives assume metabolic break-down.

Scheele *et al.* (1992) measured the concentrations of PCB-138, PCB-153, and PCB-180 in bone marrow (collected during routine bone-marrow aspiration) of 38 children with leukaemia and 15 control children (nine had idiopathic thrombocytopenia and six were bone-marrow donors). Most of the samples were pooled to ensure sufficient volume for analysis. Total PCB concentrations were determined on the basis of congeners PCB-138 + PCB-153 + PCB-180 and multiplied by 1.7 (Deutsche Forschungsgemeinschaft, 1988). The mean and median concentrations of total PCBs in bone marrow of children were 3.6 mg/kg fat basis and 2.9 mg/kg, respectively. PCB concentrations in bone marrow were two- to threefold those in fat tissue. [The reason for the high affinity of bone marrow for PCBs was not clear. It is possible that genetic factors may play a role.] There were no significant differences in PCB concentrations between the group of children with leukaemia and the control group. [The Working Group noted that the authors did not report whether parental smoking, an important confounding factor, was accounted for in their statistical analysis.]

A study in 360 schoolchildren (a subgroup of the Hesse, Germany cohort) in 1995 (Karmaus *et al.*, 2001a, b) focused on the potential of early childhood factors such as breastfeeding, parity, and parental smoking to contribute to the variety of effects observed with exposure to organochlorine compounds including PCBs, at approximately age 7 years. Concentrations of PCBs (sum of congeners PCB-101, PCB-118, PCB-138, PCB-153, PCB-170, PCB-180, PCB-183, and PCB-187) were determined in whole blood. A significant dose–dependent relationship ($P < 0.0001$) existed between the duration of breastfeeding (none, 1–4 weeks, 5–8 weeks, 9–12 weeks, > 12 weeks) and the sum of PCB concentrations. Of all the potential factors analysed, breastfeeding accounted for most of the variance in PCB concentrations. Exclusive breastfeeding beyond 12 weeks was associated with a doubling of PCB concentrations in whole blood compared with bottle-fed children (sum of PCBs, 0.25 µg/L versus 0.55 µg/L).

(ii) Experimental animals

Sixteen (eight/group) adult female rhesus monkeys were exposed to diets containing Aroclor 1248 at 2.5 or 5.0 ppm for approximately 1.5 years (Allen & Barsotti, 1976). Six out of the eight monkeys treated with Aroclor 1248 at 5.0 ppm, and eight out of the eight monkeys at 2.5 ppm were successfully bred after 6 months of exposure. One live infant was born to dams exposed at 5.0 ppm, and five infants were born to monkeys at 2.5 ppm. Infants were permitted to nurse with their mothers. All six surviving infants had PCBs

in their tissues at birth: PCB concentrations in skin biopsies (epidermis, dermis and the attached underlying subcutaneous tissue) ranged from 1.0 to 4.8 µg per g of tissue. By the third month, skin PCB concentrations ranged from 86.4 to 136.8 µg per g of tissue. The infant that died after 239 days had PCB concentrations of more than 20 µg per g in seven organs (adrenal gland, cerebrum, kidney, muscle, pancreas, testes, thymus). In the two infants that survived for shorter periods, this PCB concentration was exceeded only in three tissues (bone marrow, lung, thymus) in one infant and two tissues (bone marrow, pancreas) in the other.

Female rhesus monkeys were fed a daily dose of Aroclor 1254 (0, 5, 20, 40 or 80 µg/kg bw) for approximately 6 years (Arnold *et al.*, 1993, 1995; Mes *et al.*, 1994, 1995a). Blood and adipose tissue from offsprings exposed in utero/during lactation who had nursed for 22 weeks were analysed for PCB content at 120 weeks after birth. PCB concentrations in the adult monkeys increased with their dosage. Tissues of live infants of dosed dams contained more PCBs than those of infants of control dams, and less PCBs than those of stillborn infants. Also, offspring with higher PCB concentrations showed a marked shift from tetra- and hexachlorobiphenyls to penta- and heptachlorobiphenyls. The PCB distribution pattern in tissues from a dosed mother–infant pair differed considerably. A larger percentage of heptachlorobiphenyls was found in the infant than in its dam (Mes *et al.*, 1995a). Depletion studies revealed that PCB concentrations in the blood of exposed infants declined rapidly after weaning due to growth dilution and approached maternal levels within 40–50 weeks. Approximately 100 weeks after weaning, PCB concentrations in adipose tissue of infants from treated dams reached levels of those in the control group (Mes *et al.*, 1994).

Male Swiss mice aged 8 days were given a single intraperitoneal injection of a mixture of PCB-99, PCB-105, PCB-118, PCB-128, PCB-138, PCB-153, PCB-156, PCB-170, and PCB-180 at 500 mg/kg bw (Anderson *et al.*, 1993). Groups of 25 mice were killed at 1 and 7 days, and at 8, 12, and 16 weeks after treatment. Congeners in group 1 (PCB-99, PCB-105, PCB-118, PCB-128) were eliminated from the body more rapidly than congeners in group 2 (PCB-138, PCB-153, PCB-156, PCB-170, PCB-180). PCB concentration in the carcass (adipose compartment) was the most predictable finding, since the congeners behaved similarly within each group. In contrast, in lung, after a rapid loss during the first week, all congeners except PCB-153 were retained and decreased in amount only as a function of dilution due to growth. Congeners PCB-105 and PCB-138 were present at higher proportions in the lung than in the carcass. In the liver, retention of all congeners was observed during the prepubertal growth phase, with specific enrichment of PCB-105, followed by more rapid depletion of certain congeners (Anderson *et al.*, 1993).

(b) Effect on gene expression

Dutta *et al.* (2012) used microarray-based differential gene expression analysis of a group of children (mean age, 46.1 months) of central European descent (Slovak Republic) to study the impact of PCBs on different cellular pathways and to explain their possible mode of action. The subset of children having high blood PCB concentrations (> 75th percentile) was compared with their low PCB counterparts (< 25th percentile), with mean lipid-adjusted PCB concentrations of 3.02 ± 1.3 and 0.06 ± 0.03 ng/mg of serum lipid, respectively. A set of 162 genes with statistically significant differential expression ($P < 10^{-5}$) between groups with high and low PCB concentration was identified. Analyses using the IPA tool indicated that cell–cell signalling and interactions, cellular movement, cell signalling, molecular transport, and vitamin and mineral metabolism were the major molecular and cellular functions associated with the genes differentially expressed in children with high PCB concentrations. Furthermore, the

differential gene expression appeared to play a pivotal role in the development of probable diseases and disorders, including cardiovascular disease and cancer. The analyses also pointed out possible organ-specific effects, e.g. cardiotoxicity, hepatotoxicity and nephrotoxicity in the children exposed to high concentrations of PCBs. Expression levels of *BCL2*, paraoxonase 1 (*PON1*), interleukin *IL1F7*, *IL23A* and integrin β 1 (*ITGB1*) were significantly altered in these children; more specifically, *BCL2* and *ITGB1* were downregulated, while *IL1F7*, *PON1*, and *IL23A* were upregulated.

(c) Enzymatic effects in feto-placental unit, and fetal and neonatal liver

Alvares & Kappas (1975) investigated the induction of aryl hydrocarbon hydroxylase (Ahh) by PCBs in the feto-placental unit, fetal livers and neonatal livers during lactation. For the in-utero exposure protocol, pregnant Sprague-Dawley rats were injected intraperitoneally with Aroclor 1254 (25 mg/kg bw per day) for 6 days, and killed 24 hours later on day 20 of gestation. For the lactation experiments, untreated mothers were injected intraperitoneally with Aroclor 1254 (25 mg/kg bw per day) for 6 days starting on day 2 postpartum; the offspring of these dams were killed on day 8 postpartum.

PCBs caused a 10-fold induction in Ahh activity in the placenta, but only a threefold induction in the fetal livers. Ahh activity in placentas of untreated rats was markedly lower than that observed in the fetal liver of the same rats. In the liver of neonates whose mothers were treated with Aroclor 1254 postpartum (infants exposed through lactation), there was an 18-fold increase in Ahh activity, a threefold increase in CYP content, and a twofold increase in *N*-demethylase activity. Thus Aroclor 1254 was a more potent inducer of Ahh activity in placenta and liver when exposure occurred through lactation than through in-utero exposure when administered to pregnant rats.

4.6 Mechanistic considerations

The group of PCBs comprises 209 individual congeners with widely different physical and chemical properties. The number of chlorine atoms on the two phenyl rings and their relative positions determine the biological and toxicological attributes of each congener. Some PCBs are susceptible to metabolic conversion, which may give rise to a series of metabolites, each with its own profile of biological and toxicological activities. In this section, various mechanisms of carcinogenesis will be identified and summarized for specific subgroups of PCBs and their metabolites.

4.6.1 Metabolic activation and genotoxicity of PCBs and their metabolites

(a) Metabolism leading to formation of electrophiles

The 209 PCB congeners vary greatly in their susceptibility to metabolic attack, with less chlorinated biphenyls being much more susceptible. The first metabolic step is mono-oxygenation, which leads to the formation of hydroxylated metabolites, a reaction that is mediated by enzymes of the CYP super-family. There are 837 possible mono-hydroxylated products (Rayne & Forest, 2010; Grimm *et al.*, 2015). Depending on the number of chlorines present, the arene oxide may emerge as a highly reactive, electrophilic species: the lower the number of chlorines, the more reactive the arene oxide.

Mono-hydroxylated PCBs may undergo a second hydroxylation, producing a dihydroxylated PCB derivative, either as catechol (hydroxyl groups in the *ortho* configuration) or as hydroquinone (hydroxyl groups in the *para* configuration) (McLean *et al.*, 1996a). The formation of dihydroxylated PCBs is catalysed primarily by CYP enzymes. PCB catechols and hydroquinones may then be oxidized by peroxidases, prostaglandin synthase, and probably other enzymes,

giving rise to the formation of highly reactive electrophilic PCB quinones (Amaro *et al.*, 1996; Oakley *et al.*, 1996a; Wangpradit *et al.*, 2009).

The oxygenated PCB intermediates and metabolites, i.e. the arene oxides and the quinones, are probably the most relevant to PCB-induced carcinogenesis, but many other metabolites may also be formed. For example, OH-PCBs are substrates for glucuronidation (Tampal *et al.*, 2002) and sulfation (Liu *et al.*, 2006, 2009; Ekuase *et al.*, 2011). All electrophilic PCB metabolites with elevated chemical reactivity, however, should be regarded as probable cancer initiators.

(b) Binding to DNA and protein

Covalent binding to cellular macromolecules (adduct formation) has been observed in mice treated with radiolabelled PCB-153 and PCB-136, the binding of the latter decreasing in the order RNA > protein > DNA (Morales & Matthews, 1979). Formation of protein and DNA adducts was observed in vitro with PCB-3 and the tetrachlorinated congeners PCB-47, PCB-49, PCB-52, and PCB-77 (Wyndham *et al.*, 1976; Shimada & Sawabe, 1984). DNA-adduct formation was also observed with a series of 15 mono- and dichlorinated PCBs, with but not without activation by microsomes, horseradish peroxidase and hydrogen peroxide (McLean *et al.*, 1996b). This suggested that quinones were the ultimate genotoxic agents. Indeed, tests with synthetic quinones of less chlorinated PCBs confirmed the extensive DNA-adduct formation, particularly with deoxyguanosine (Oakley *et al.*, 1996a; Zhao *et al.*, 2004).

These experiments indicated that PCBs require CYP-mediated metabolic activation, that a lower degree of chlorination favours bioactivation, that an arene oxide intermediate and/or possibly a semiquinone or quinone is the ultimate DNA-binding species, and that guanine is the major target site in DNA. Apart from binding to DNA, PCB quinones also bind cellular proteins, preferably, but not exclusively, to cysteine (Amaro *et al.*, 1996; Srinivasan *et al.*, 2002; Bender *et al.*, 2006).

(c) Indirect genotoxicity: metabolism-associated generation of ROS

The arene oxides and quinones are probably the metabolites with most relevance to the cancer-initiating activity of PCBs, since they can be regarded as direct-acting genotoxic intermediates. In addition, dihydroxylated PCBs and their corresponding PCB quinones may undergo redox cycling, thereby generating ROS, which are considered to be active in the initiation, promotion, and progression of cancer. For example, ROS formed during auto-oxidation of a PCB hydroquinone may give rise to oxidative DNA damage, e.g. 8-OHdG. Mutations induced by these lesions may lead to activation of oncogenes or inhibition of tumour-suppressor genes, thus contributing to the carcinogenic potential of PCBs (Amaro *et al.*, 1996; Oakley *et al.*, 1996a). Formation of ROS may also induce DNA strand breaks (Srinivasan *et al.*, 2001).

(d) Mutagenic effects

PCB-3, 4-OH-PCB-3, and two hydroquinones of PCB-3 were tested for mutagenicity in Big Blue® rats and in Chinese hamster V79 cells. These results demonstrated that monochlorinated PCBs are mutagenic in vivo in the target organ, the liver, and studies in vitro suggested that metabolic activation to electrophilic and mutagenic species plays a crucial role. Although the ultimate mutagenic metabolite (*ortho*- or *para*-quinone, or epoxide or other metabolite) could not be deduced with certainty, the evidence pointed towards adduct formation by a quinone, or quinone-induced redox cycling as the mode of action.

Apart from gene mutations, other forms of genotoxicity observed after exposure to PCBs included the induction of DNA strand breaks, and anomalous segregation of chromosomes.

Elevated concentrations of mono- and dihydroxylated metabolites of PCB-3 were shown to induce these types of lesions in vitro (Zettner *et al.*, 2007; Flor & Ludewig, 2010).

With regard to the PCB congeners considered to act primarily through *trans*-activation of nuclear receptors, the available data provided little evidence regarding genotoxicity (see Section 4.2).

(e) Cancer initiation and promotion

The ability of commercial PCB mixtures and individual PCB congeners to initiate and/or promote neoplastic lesions has been studied in rodent two-stage models of liver carcinogenesis. Aroclor 1254, which contains mainly tetra- and pentachlorobiphenyls, acted as a weak tumour initiator in the mouse two-stage model of skin carcinogenesis (DiGiovanni *et al.*, 1977). In contrast, when tested using the Solt-Farber protocol, Aroclor 1254 and the PCB-153, PCB-52, and PCB-47 did not produce a positive response in male F344 rats (Hayes *et al.*, 1985). No nodules were apparent in animals receiving PCB-12 (dichloro-) or PCB-138 (trichloro-) as initiator, while PCB-3 (mono-chlorinated) induced clearly visible nodules in 50% of the exposed rats (Espandiari *et al.*, 2003). Thus less chlorinated PCBs seem to be able to initiate hepatocarcinogenesis in the rat, but in view of the small number of congeners tested, a clear structure–activity relationship could not be established.

A series of synthetic oxygenated metabolites of PCB-3 were studied with respect to focus formation in rat liver. Test compounds included the 2-OH-, 3-OH-, 4-OH-, 2,3-dihydroxyl-, 3,4-dihydroxyl-, 2,5-dihydroxyl-, 2,3-quinone, 3,4-quinone, and 2,5-quinone metabolites of PCB-3. The 4-OH- and 3,4-quinone metabolites significantly increased focus number and focus volume, while none of the other metabolites had a significant effect on either parameter (Espandiari *et al.*, 2004, 2005). The 3,4-*ortho*-quinone of PCB-3 was the initiating metabolite, and that PCB-3 is metabolized in rat liver in vivo to yield this ultimate carcinogenic species.

(f) Direct and indirect endocrine disruption

After the liver, the thyroid gland is the second major target of the toxicity of PCBs. In rats, exposure to PCBs produced an increase in the mass and/or volume of the thyroid gland, and in the number of thyroid neoplasms (Mayes *et al.*, 1998). Both these changes may be linked to the PCB-driven reduction in serum T4 concentrations, a commonly measured effect of PCBs (Knerr & Schrenk, 2006; Pearce & Braverman, 2009). Suggested mechanisms include: (a) PCB-induced alterations in the structure and function of the thyroid gland; (b) PCB-induced alterations in thyroid-hormone metabolism, biliary excretion of T4-glucuronide (Martin *et al.*, 2012), and effects on de-iodonase activity; and (c) interference with the transport of T4. OH-PCBs are competitors for the T4-binding site in the transport protein TTR (Brouwer *et al.*, 1998; Gutleb *et al.*, 2010), with binding affinities up to an order of magnitude stronger than that of the natural ligand, T4 (Chauhan *et al.*, 2000). The sulfate conjugates of OH-PCBs also bind to TTR, with affinities similar to that of T4 (Grimm *et al.*, 2012).

Circulating steroid and thyroid hormones are sulfated by sulfotransferases, which is an important feature of their homeostatic control. Since OH-PCBs are both substrates and inhibitors of these enzymes, they may directly influence the circulating levels of steroids and thyroid hormones by affecting the rates of sulfation (Schuur *et al.*, 1998b, c; Kester *et al.*, 2000; Liu *et al.*, 2009; Ekuase *et al.*, 2011).

OH-PCBs have both estrogenic and anti-estrogenic properties (see Section 4.3.3).

4.6.2 Receptor-driven effects of PCBs and their metabolites

PCBs and their metabolites may bind to and activate a wide range of cellular receptors, as illustrated in Table 4.8. Activation of AhR, CAR, and other receptors results in extensive modulation of expression of genes involved in cell-cycle control, cell proliferation, apoptosis, cell–cell communication, cell adhesion and migration, the pro-inflammatory response, and endogenous metabolism. Deregulation of those processes is directly associated with carcinogenesis, i.e. tumour promotion and progression (see Sections 4.3.1 and 4.3.2). The most significant events include modulation of cell proliferation, suppression of apoptosis (i.e. survival of initiated cells), impaired plasma-membrane function and plasma membrane-mediated signal transduction (i.e. modulation of cell plasticity, cell–cell communication, adhesion and migration) and induction of proinflammatory mediators. In part, induction of cell proliferation may be a consequence of cytotoxicity and tissue injury – after biotransformation processes, oxidative stress, etc. – and is considered regenerative cell proliferation (see Section 4.3.2).

In addition, disruption of endocrine function, due to interaction of PCBs or their metabolites with steroid and thyroid hormone receptors and serum proteins, or as a result of changes in biosynthesis and catabolism of steroids, may be linked to cancer development in hormone target tissues (see Section 4.3.3). Receptor-mediated gene expression is also linked to induction of proinflammatory processes and immunotoxic effects (see Sections 4.3.4 and 4.3.5).

(a) Induction of xenobiotic metabolism

Many highly chlorinated PCB congeners are potent inducers of enzymes involved in the metabolism of xenobiotics (Parkinson *et al.*, 1983) via binding to AhR (Bandiera *et al.*, 1982). Efficient induction has been reported of a wide spectrum of enzymes, notably certain CYP-dependent mono-oxygenases of the CYP1A subfamily, as well as CYP2Bs and microsomal epoxide hydrolase (Parkinson *et al.*, 1983), glutathione transferases, and UDP-glucuronosyl transferases (for a review, see Parkinson *et al.*, 1980).

Individual PCB congeners that showed the strongest binding to the AhR were identified as those in which the chlorines are in the *meta* and *para* positions of the phenyl rings in the absence of *ortho* chlorines (see Section 1.1.1). These PCBs are referred to as "coplanar" or "dioxin-like," typical examples being PCB-77, PCB-126, and PCB-169. Other PCBs, characterized by substitution in the *ortho* and *para* positions of the phenyl rings (e.g. PCB-153), activate CAR. PCBs in this group induce CYP2B1/2 and other enzymes, and as such resemble the drug phenobarbital (Parkinson *et al.*, 1983). Many PCBs that activate CAR also activate the pregnane X receptor (Holsapple *et al.*, 2006). PCBs that have one chlorine in the *ortho* position may be mixed-type inducers of CYPs, for example PCB-118, which induces members of the CYP1A and the CYP2B subfamilies.

Exposure to PCBs may alter the metabolic status in the liver, which will change the metabolism of endogenous or other exogenous compounds. For example, PCBs induce CYPs in the liver, which may redirect the metabolism of endogenous estrogen to more harmful estrogen catechols (Ho *et al.*, 2008), or generate ROS that produce estrogen quinones (Brown *et al.*, 2007).

(b) Immunomodulation

The biochemical events leading to the observed PCB-induced immunomodulation have not been completely elucidated. Studies on structure–activity relationships, and structure–toxicity relationships have demonstrated that some of the PCBs share a common mechanism of action with other structurally related halogenated aromatic hydrocarbons such as dioxins and dibenzofurans (Safe, 1990). These studies

Table 4.8 PCBs and metabolites as ligands for cellular and nuclear receptors

Receptor		Ligands	Gene or function affected	References
AhR	Aryl hydrocarbon	Coplanar, ***meta***-, ***para***-PCBs	CYP1A activation	Bandiera *et al.* (1982)
CAR	Constitutive androstane receptor	*Ortho*-, *para*-PCBs	CYP2B activation	Denomme *et al.* (1983), Al-Salman & Plant (2012)
PXR	Pregnane X receptor	Multi-*ortho*-PCBs, PCB-47, PCB-184; PCB-138, PCB-153, PCB-180, PCB-194	CYP3A activation	Schuetz *et al.* (1998), Al-Salman & Plant (2012)
PPAR	Peroxisome proliferator receptor	Coplanar, *meta*-, *para*-PCBs	CYP4A, repression	Hennig *et al.* (2005), Robertson *et al.* (2007)
RyR	Ryanodine receptor	Non-dioxin-like-PCBs (optimal configuration, multi-*ortho*, *para*-PCBs), OH-PCBs, catechols, $MeSO_2$-PCBs	Ca^{2+}-channel	Pessah *et al.* (2006)
ER	Estrogen receptor	Multi-*ortho*-PCBs, OH-PCBs	Agonism and antagonism	Connor *et al.* (1997), Arcaro *et al.* (1999); Bonefeld-Jørgensen *et al.* (2001), Plísková *et al.* (2005), Hamers *et al.* (2011)
AR	Androgen receptor	Multi-*ortho*-PCBs	Antagonism	Portigal *et al.* (2002), Fang *et al.* (2003); Schrader & Cooke (2003), Hamers *et al.* (2011)
PR	Progesterone receptor	OH-PCBs	Antagonism	Connor *et al.* (1997)
TH	Thyroid hormone	PCBs, OH-PCBs	Disruption of thyroid receptor-dependent gene expression	Gauger *et al.* (2004), Miyazaki *et al.* (2004)
DAT or VMAT	Dopamine active transporter or vesicular monoamine transporters	Coplanar and multi-*ortho*-PCBs	Decrease or increase in dopamine levels	Bemis & Seegal (2004), Richardson & Miller (2004), Seegal *et al.* (2005)
GR	Glucocorticoid receptor	$MeSO_2$-PCBs, OH-PCBs, PCB-28, PCB-153, PCB-118	Competitive antagonism	Johansson *et al.* (1998), Bovee *et al.* (2011), Antunes-Fernandes *et al.* (2011)

$MeSO_2$-PCB, methyl sulfonyl PCB; OH-PCB, hydroxylated PCB; PCB, polychlorinated biphenyl
Adapted from Ludewig *et al.* (2007)

indicated that certain immunotoxic effects seen with dioxin-like PCB congeners depend on the presence of AhR, which regulates the synthesis of a variety of proteins (Safe, 1990). AhR is present in several tissues and cells of the immune system as shown in rodents (e.g. Mason & Okey, 1982), in non-human primates (Van Der Burght *et al.*, 1998) and in humans (Hakkola *et al.*, 1997).

AhR is present in several tissues and cells of the immune system in animals and in humans. Binding of PCBs to AhR is a prerequisite for some of the immunotoxic effects of the DL-PCBs (reviewed in Silkworth *et al.*, 1984; Safe, 1990). TEFs were calculated for individual PCB congeners and several commercial PCB products, based on the suppression of the response in a challenge test against sheep erythrocytes (SRBC) – a parameter predictive of effects on humoral immunity (Davis & Safe, 1989, 1990). Highly chlorinated commercial PCB products, including Aroclors 1260, 1254, and 1248 have higher TEFs, while lower TEFs were calculated for the less chlorinated Aroclors 1242, 1016, and 1232.

Clearly some PCBs produce their immunotoxic effects by binding to AhR present in tissues and cells of the immune system, while others may follow different pathways and produce similar effects. Furthermore, individual congeners in commercial PCB products may antagonize each other's effects by mechanisms that have not been fully elucidated (see Section 4.3.4).

Overproduction of IL-6 has been shown to be responsible for the pathogenesis of inflammation-associated colorectal cancer (Waldner *et al.*, 2012). Furthermore, activation of NF-κB, a hallmark of inflammatory responses, plays a fundamental role in the formation and development of malignant tissue changes caused by inflammation, and is thought to function as a tumour promoter in inflammation-associated cancer (Pikarsky *et al.*, 2004; Karin, 2006).

(c) Interference with endogenous transport by PCBs and their metabolites

Endogenous substances such as vitamins, metals, steroids, and hormones are transported throughout the body by virtue of their binding to serum proteins. Substances that interfere with these processes can severely impair their tissue availability. Notable examples are the ability of PCB metabolites to interfere with vitamin A homeostasis and T4 transport (Grimm *et al.*, 2012), and steroid metabolism (see Section 4.3.3).

Overall, PCBs can induce formation of ROS, genotoxic effects, immune suppression, inflammatory responses, and endocrine effects to various extents and through different pathways. DL-PCBs exert their effects mainly through activation of AhR and the downstream cascade of related events; less chlorinated PCBs act more readily through metabolic activation and the ensuing effects involving their metabolites.

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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

Polychlorinated biphenyls (PCBs) are a class of aromatic chemical compounds in which some or all hydrogen atoms attached to the biphenyl nucleus are substituted by one to ten chlorine atoms. There are 209 congeners, which are arranged according to current nomenclature from 1 to 209 by increasing number of chlorines. Although physical and chemical properties vary widely across the class, PCBs generally have low solubility in water, high lipophilicity, and low vapour pressure; they are chemically stable and generally persist in the environment and in the human body.

PCBs are not known to occur naturally and have been produced commercially by a limited number of companies since 1929. Production peaked between the 1950s and the 1970s, and was banned in most countries by the 1980s; however, manufacturing in the Democratic People's Republic of Korea continued at least until 2006.

Commercial PCB products were manufactured to yield a given degree of chlorination to fulfil technical requirements. Products sold under different trade names (e.g. Aroclor, Clophen, Kanechlor) may be of similar composition with regard to the chlorine content. However, individual congeners have generally not been quantified in these products. A subset of PCBs are referred to as "dioxin-like PCBs," and have been assigned toxicity equivalency factors (TEFs) relative to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD).

Laboratory analyses of PCBs have improved in selectivity and sensitivity through the development of advanced instrumentation and analytical strategies allowing the identification and quantification of individual congeners within commercial products. State-of-the-art analytical methods enable detection of PCBs in virtually all types of sample; however, comparability with older methods is limited. Dioxin-like PCBs often occur in lower concentrations than other PCBs and are analysed together with polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Apart from instrumental analysis, analyses based on biological response have been applied as screening tools.

Based on their physical and chemical properties, such as non-flammability, chemical stability, high boiling point, and high dielectric constant, products containing PCBs were widely used in several industrial, commercial, and military open and closed applications. The most important closed applications were as dielectric fluids in capacitors and transformers, and as hydraulic fluid and heat-transfer medium. Although these applications are considered as "closed," PCBs can still be released into the environment due to leakage. The most important open applications were as constituents of permanent elastic sealants, in polymers, and as flame-retardant coatings. To a lesser extent, PCBs were also used in inks, adhesives, dyes for carbonless duplicating paper, conveyor belts, and other rubber products, small ballasts for fluorescent lights, cutting

and lubricating oils, and metal coatings. In all open applications, PCBs can be released from the product into the environment via volatilization or erosion.

Once released into the environment, PCBs can be transported via environmental media and migratory species far from the site of production and use. PCBs are ubiquitous in the environment and are found in biota, air, soil, sediment, and water worldwide, including in polar regions and deep oceans. PCB concentrations vary by several orders of magnitude. Furthermore, congener patterns differ to varying degrees in air, water, sediments and soils as a consequence of transport, and transformation processes such as dechlorination. In the environment, PCBs volatilize easily, or are ingested by fish and other animals and transferred to the food chain, where their concentration may increase.

The general population is exposed primarily through ingestion of contaminated food. Food can become contaminated with PCBs by: (i) uptake from the environment by fish, birds, livestock; (ii) contamination of the foodstuffs through usual practice or industrial processing; and (iii) accidental contamination. In contrast to vegetables and crops, fatty foods typically contain high concentrations of PCBs. Most foodstuffs will have a shift in the congener profile in favour of less volatile, more highly chlorinated congeners.

Six congeners (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180) are found at high concentrations in the environment, food, and in human tissue. These congeners are often used to monitor exposure in epidemiological studies and are referred to as "indicator PCBs."

There have been two major episodes of human food contamination; both of which occurred in Asia; these episodes are commonly referred to as "Yusho" and "Yucheng." These populations were exposed through accidental contamination of cooking oil with either Kanechlor 400 or Kanechlor 500. Exposed people had blood PCB concentrations that were 100 to 1000 times higher than in the non-exposed population. Other accidental releases have occurred in the last few decades.

Indoor air can also contribute to human exposure to PCBs, owing to the use of PCBs in construction material. Exposure can occur in the workplace or at home; importantly, children may be exposed in schools and nurseries where PCB-containing materials have been used. Inhalation of PCBs results in a higher relative exposure to the more volatile, less chlorinated congeners.

Workers may be exposed during manufacturing, repair, use, and disposal of products or equipment containing PCBs. Earlier exposures to PCBs were higher and occurred during PCB manufacture, and filling of PCB-containing transformers and capacitors (up to 11 000 μg/m^3) and during the repair of transformers (up to 60 μg/m^3). More recent exposures may occur during abatement in construction (up to 120 μg/m^3), waste incineration, and recycling of electronic equipment and – to a lesser extent – working in PCB-contaminated buildings (up to 10 μg/m^3). It has been reported that workers in small-scale welding facilities in less developed countries may not use personal protective equipment when extracting PCB-contaminated coolant oil from discarded transformers, and are therefore likely to receive a considerable degree of exposure.

Historically, workers were exposed through inhalation and dermal contact, while occupational exposure to PCBs is nowadays primarily through dermal contact. In the past, workers were exposed during PCB manufacture and use to congener patterns that were similar to those of the products they handled, while today's workers are exposed to congener profiles that are different from those of the commercial mixtures. Occupational exposures to PCBs before the banning of PCB manufacture in the 1980s were much higher than those encountered today from

other sources. Since then, levels of occupational exposure to PCBs have been greatly reduced and now approach levels of environmental exposure.

5.2 Human carcinogenicity data

The association between exposure to PCBs and risk of cancer in humans has been evaluated in a large number of epidemiological studies in several occupational groups, in populations with elevated exposure to PCBs as a result of environmental incidents, and in the general population. Studies have been conducted in several countries, primarily in North America, Europe, and Asia, and have used cohort, nested case–control, and case–control designs.

The Working Group considered more than 70 separate studies with informative data regarding several cancer sites. The most important evidence regarding carcinogenicity came from studies of workers in industries where PCBs were used, and from population-based case–control studies. Occupational studies assessed exposure to PCB mixtures through job-exposure matrices and historical measurements, but most did not report data on non-occupational risk factors, which are important for some cancer sites. In case–control studies, analyses included adjustments for a larger range of risk factors and most used measurements of PCB concentrations (typically for specific congeners or groups of congeners) in blood or adipose tissue as indicators of exposure. The Working Group did not consider any exposure-assessment approach to be superior, each providing contrasting but useful information.

5.2.1 Malignant melanoma

Information on the association between risk of melanoma and exposure to PCBs was available primarily from cohort studies of capacitor- and transformer-manufacturing workers (four studies) and electric power and equipment workers (three studies) in North America and Europe. Excess risks of melanoma were reported in all studies except one. The only study reporting null results combined data from two plants in the USA: risk was significantly increased in the plant with predominantly white workers, but not in the second, where a large proportion of workers of African heritage were employed. Exposure–response relationships were evaluated in three studies and a statistically significant linear exposure–response trend was observed with a 20-year lag in the largest study, which included workers at five electric power companies.

Further evidence came from a high-quality case–control study of skin melanoma in Canada, which reported measurement of plasma concentrations of PCBs. This was the only case–control study in which the association between PCBs and melanoma was evaluated in the general population; the study used biological measurements of exposure and accounted for potential confounding factors. Trends were evaluated for dioxin-like PCBs, non-dioxin-like PCBs, and eight highly chlorinated individual congeners: all trends were positive and statistically significant. Additional support came from a multicentre European case–control study of uveal melanoma that assessed occupational exposure to oils containing PCBs and found positive associations.

The association between malignant melanoma and exposure to PCBs was consistently observed across studies of occupational exposure in different industries in several countries, in the general population, and with both cohort and case–control designs. These findings were unlikely to be a result of chance, since statistically significant associations were observed in large studies. Exposure–response relationships were also observed in several studies using different methodologies among exposed workers and in the general population. Confounding or other bias is unlikely to explain these results: there are few known risk factors for malignant melanoma other than sunlight, which was controlled for in

the case–control studies and in the only large study of occupational exposure that included outdoor workers for whom occupational exposure to sunlight could be significant. Exposure to sunlight is unlikely to confound associations in studies of indoor workers, since there is no reason to believe that exposure to sunlight during leisure time is associated with occupational exposure to PCBs.

5.2.2 Non-Hodgkin lymphoma

Data on the association of NHL and exposure to PCBs are available from studies of five independent occupational cohorts of capacitor manufacturing workers (three in the USA, one each in Italy and Sweden) and two cohorts of transformer manufacturing and repair workers (one in the USA, one in Canada). Four of these studies included specific assessments of the level of PCB exposure (three in the USA, one in Sweden). Statistically significant increases in mortality from NHL were observed in a cohort of capacitor manufacturing workers in Italy and among retired workers at a transformer manufacturing plant in the USA. Non-statistically significant increased risk of NHL was observed in the other capacitor and transformer manufacturing cohorts. However, a separate analysis of one of these latter cohorts by different investigators reported no excess of NHL. None of the four studies that assessed the level of PCB exposure found clear evidence of an exposure–response relationship The number of deaths from non-Hodgkin lymphoma was above that expected among men (deaths, $n = 4$) in a mortality follow-up study of a population in Taiwan, China, as a result of a mass poisoning episode with cooking oil contaminated with PCBs (Yucheng). However, no data on non-Hodgkin lymphoma were reported after a similar episode in Japan (Yusho), with a different exposure profile.

Nested case–control studies were conducted among subsamples of large population cohorts, and presented the advantage of having collected blood at recruitment, and having subsequently identified incident cases. Statistically significant trends in risk were associated with the sum of PCB congeners in three of the five studies considered; and were positive with specific congeners in several studies.

Four out of six good-quality case–control studies provided indications of a positive trend in risk of non-Hodgkin lymphoma with increasing plasma concentrations of the sum of PCBs. The results of a European case–control study of non-Hodgkin lymphoma were null overall, although heterogeneity was observed across the participating centres. A positive interaction was reported with markers of infection with Epstein-Barr virus (EBV), or with polymorphisms in genes encoding inflammatory cytokines, or an ancestral haplotype for human leukocyte antigen (HLA). Regarding non-Hodgkin lymphoma subtypes, follicular lymphoma, but not diffuse large B-cell lymphoma, was positively associated with exposure to PCBs in three studies.

In summary, the balance of evidence, taking into account study size and quality, suggested increased risk of non-Hodgkin lymphoma in relation to PCB exposure, and this is biologically plausible. However, since heterogeneous results were observed in high-quality studies, the Working Group could not exclude chance as a potential explanation for the associations observed. It is noteworthy that bias and confounding were excluded.

5.2.3 Cancer of the breast

Many studies investigated the risk of cancer of the breast in relation to exposure to PCBs, with the rationale that such an association is biologically plausible. The evidence that weighed most strongly in this evaluation came from 12 well designed and implemented case–control studies in the USA, Canada, and Japan that assessed risk in relation to concentrations of PCBs measured

in serum and/or adipose tissue. These studies each included between 175 and 750 cases of cancer of the breast, the controls being comparable women without cancer of the breast, and results were adjusted for relevant confounders. In one large study in the USA, no excess risk was seen, while in the other large study in the USA, increased risk of cancer of the breast in relation to PCBs was seen among African-American women, and among parous never-lactating white and African-American women combined. Of the 10 moderately sized studies, increased risks were seen in six studies in relation to PCBs, with some exposure–response relationships. In some of these studies, risk was also evaluated by subgroup, and increased risks were seen for women who were parous and had never lactated, for pre- and postmenopausal women, by various tumour characteristics, and by *CYP1A1* variants. Statistically significant increases in risk ranged from 1.1- to 4.3-fold. Three additional moderately sized studies from the USA reported no excess risk, while an inverse risk was seen in one study from Japan. Two additional case–control studies assessed PCBs through estimates of occupational or dietary exposure, and although the results suggested some increase in risk, these studies were not weighted strongly. In addition, most of the 10 smaller case–control studies reported some increased risks in relation to PCBs, although they were not weighted strongly in this evaluation due to the imprecise risk estimates.

While a few cohort studies of occupational exposure suggested an increased risk of cancer of the breast, PCB exposure was usually not assessed quantitatively in relation to risk, and important potential confounders were not taken into account. Within a case–control study nested among female capacitor workers, increased risk of cancer of the breast was seen for "non-white" (otherwise unspecified) women, taking into account non-occupational confounders. Other nested case–control studies (six from the USA, two from Denmark, and one from Norway) had a small or moderate number of cases and assessed PCBs in serum or adipose tissue with controls for confounders. The findings suggested some increased risks associated with some of the PCBs analysed, but the studies had limited power to assess associations.

On the balance of evidence, when taking into account study size, quality, and magnitude of risk, an increased risk of cancer of the breast was seen in relation to PCBs, with higher risks among some subgroups, and these associations are biologically plausible. Bias and confounding are unlikely to explain these results. However, as the results across high-quality studies were heterogeneous, the Working Group could not exclude chance as a possible explanation for positive associations.

5.2.4 Other cancer sites

Several other cancer sites were considered in one or more cohort or case–control studies. There were positive findings for cancer of the prostate and brain in several studies, but null findings in others. Other cancers with sporadic positive findings were those of the liver and biliary tract, extrahepatic biliary tract, lung and respiratory tract, thyroid, stomach, pancreas, colon and rectum, urothelial organs, uterus and ovary combined, as well as childhood acute lymphatic leukaemia, and multiple myeloma.

5.3 Animal carcinogenicity data

PCBs (individual congeners, binary mixtures, and commercial mixtures) were evaluated in rats and mice in studies of various design, and ranging in duration from several months up to 2 years. These included 2-year studies of carcinogenicity, studies involving transplacental/perinatal and postnatal exposure, initiation–promotion studies examining the promoting activity, and other co-carcinogenicity studies, using tumours as an end-point.

For the 2-year bioassays, the route of administration was oral, by gavage or feeding. In studies of initiation–promotion, co-carcinogenicity, and transplacental/perinatal exposure, PCBs were also administered intraperitoneally, subcutaneously, or by skin application. There were no studies of exposure by inhalation.

5.3.1 PCB congeners

PCB-126 was tested for carcinogenicity in one study in female rats treated by gavage. PCB-126 caused significant increases in the incidences of benign and malignant tumours of the liver (hepatocellular adenoma, hepatocholangioma, and cholangiocarcinoma), lung (cystic keratinizing epithelioma), and oral mucosa (gingival squamous cell carcinoma). In two studies of transplacental/perinatal exposure in female rats treated by gavage, PCB-126 had an inhibitory effect on the development of tumours of the mammary gland induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) in the offspring.

PCB-153 was tested for carcinogenicity in one study in female rats treated by gavage, one 4-month study of perinatal exposure in mice (including an initiation–promotion experiment), and one initiation–promotion study in mice. In the study of carcinogenicity, PCB-153 did not cause significant increases in the incidence of tumours in rats, but two rare cholangiomas were observed. PCB-153 promoted hepatocellular carcinomas induced by *N*-nitrosodiethylamine (NDEA) in mice. PCB-153 did not induce or promote bronchioloalveolar tumours in mice. PCB-153 was also evaluated as part of a binary mixture in a study examining the effect of increasing the dose of PCB-153 on the carcinogenicity of PCB-126 (see below); increasing the dose of PCB-153 increased the incidences of hepatocellular adenoma and cholangiocarcinoma when coadministered with PCB-126.

PCB-118 was tested for carcinogenicity in one study in female rats treated by gavage. PCB-118 caused significant increases in the incidences of benign and malignant tumours of the liver (hepatocellular adenoma, hepatocholangioma, and cholangiocarcinoma), benign tumours of the lung (cystic keratinizing epithelioma), and carcinoma of the uterus.

A binary mixture of PCB-126 and PCB-153 was tested for carcinogenicity in one study in female rats treated by gavage. The mixture of PCB-126 and PCB-153 caused significant increases in the incidences of hepatocellular adenoma, hepatocholangioma and cholangiocarcinoma, cystic keratinizing epithelioma of the lung, and squamous cell carcinoma of the oral mucosa. As stated above, increasing the proportion of PCB-153 to PCB-126 caused significant increases in the incidences of hepatocellular adenoma and cholangiocarcinoma in one study.

A binary mixture of PCB-118 and PCB-126 was tested for carcinogenicity in one study in female rats treated by gavage. The mixture caused significant increases in the incidences of hepatocellular adenoma, cholangiocarcinoma, and cystic keratinizing epithelioma of the lung.

When given to mice for 4 months, from the perinatal period to adulthood, PCB-138 was not carcinogenic, but did show evidence of a promoting effect based on a significant increase in the multiplicity of bronchioloalveolar adenomas induced by *N*-nitrosodimethylamine (NDMA).

A mixture of PCB-138 and PCB-153 was administered to mice for 4 months, from the perinatal period to adulthood. The mixture was not carcinogenic, and did not promote bronchioloalveolar tumours.

A mixture of non-*ortho*, mono-*ortho*, and di-*ortho* substituted PCB congeners, *p,p′*-dichlorodiphenyltrichloroethane (DDT) and *p,p′*-dichlorodiphenyldichloroethene (DDE) was tested for carcinogenicity in one study of perinatal exposure in rats treated by gavage. The mixture was not carcinogenic.

The hydroxylated mono-*ortho*-PCBs 2′,4′,6′-trichloro-4-biphenylol (4′-OH-PCB-30) and 2′,3′,4′,5′-tetrachloro-4-biphenylol

(OH-PCB-61), alone or as a binary mixture, were tested for carcinogenicity in one study of perinatal exposure in female mice treated by subcutaneous injection. Both the individual congeners and the binary mixture caused a significant increase in the total incidence of malignant tumours of the cervicovaginal tract (squamous cell carcinomas and adenosquamous carcinomas).

A mixture of the three non-*ortho* congeners PCB-77, PCB-126, and PCB-169, six polychlorinated dibenzodioxins, and seven polychlorinated dibenzofurans was tested for carcinogenicity in one study of perinatal exposure in female rats treated by gavage. The mixture caused a significant increase in the incidence of benign lesions of the mammary gland (hyperplasia, adenoma, and fibroadenoma).

A mixture of PCB-126, TCDD, and 2,3,4,7,8-pentachlorodibenzofuran was tested for carcinogenicity in one long-term study in female rats treated by gavage. The mixture caused a significant increase in the incidence of benign and malignant tumours of the liver (hepatocellular adenoma and cholangiocarcinoma) and benign tumours of the lung (cystic keratinizing epithelioma).

5.3.2 Aroclor

In a feeding study of carcinogenicity in male and female rats, Aroclor 1016 caused significant increases in the incidence of hepatocellular adenoma, and of hepatocellular adenoma or carcinoma (combined) in female rats.

In a feeding study of carcinogenicity in male and female rats, Aroclor 1242 caused significant increases in the incidence of hepatocellular adenoma in female rats, and of thyroid follicular cell adenoma, and thyroid follicular cell adenoma or carcinoma (combined) in males.

Aroclor 1254 was tested for carcinogenicity in two feeding studies in male and female rats, one feeding study in male mice, three studies of transplacental/perinatal exposure in mice, two studies examining promoting activity in male rats, five studies examining promoting activity in mice, and three co-carcinogenesis studies in mice. In rats, oral administration of Aroclor 1254 caused significant increases in the incidence of hepatocellular adenoma or carcinoma (combined) in males in the first study, and of hepatocellular adenoma and hepatocellular carcinoma in females, and of thyroid follicular cell adenoma, and follicular cell adenoma or carcinoma (combined) in males in the second study. In mice, oral administration of Aroclor 1254 caused significant increases in the incidence of "hepatomas" of the liver. In the studies of transplacental/perinatal exposure, Aroclor 1254 was not carcinogenic in mice, but promoted NDMA-induced bronchioloalveolar adenomas in two studies, and coalescing liver tumours in one study. In rats, Aroclor 1254 promoted NDEA-induced hepatocellular carcinomas in one study. In mice, Aroclor 1254 promoted NDEA-induced hepatocellular adenomas in one study, and NDEA-induced hepatocellular carcinomas, hepatoblastomas, and cholangiocellular tumours in another study. In a third study, Aroclor 1254 promoted lung tumours induced by NDMA and by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Aroclor 1260 was tested for carcinogenicity in one feeding study in male rats, one feeding study in female rats, and two feeding studies in male and female rats. Aroclor 1260 caused significant increases in the incidences of "liver tumours" in males in one study, and of hepatocellular adenoma and carcinoma in females in a second study. In a third study, Aroclor 1260 increased the incidence of hepatocellular carcinoma in females, and of cholangioma in males and females. In a fourth study, Aroclor 1260 increased the incidence of hepatocellular adenoma in males, of hepatocellular adenoma, hepatocellular carcinoma, and cholangioma in

females, and of thyroid follicular cell adenoma in males.

5.3.3 Clophen

In one feeding study of carcinogenicity in male rats, Clophen A 30 caused a significant increase in the incidence of benign hepatocellular tumours.

In one feeding study of carcinogenicity in male rats, Clophen A 60 caused significant increases in the incidence of benign hepatocellular tumours and hepatocellular carcinoma.

5.3.4 Kanechlor

Kanechlor 300 gave negative results when tested for carcinogenicity in one feeding study in male and female mice, and one feeding study in male mice.

Kanechlor 400 was tested for carcinogenicity in one feeding study in male and female mice, one feeding study in male mice, and one feeding study in male and female rats. Kanechlor 400 was also tested in three initiation–promotion studies examining promoting activity, one in rats and two in mice. Both studies of carcinogenicity in mice gave negative results. The results of the study of carcinogenicity in rats were inconclusive. Kanechlor 400 promoted hepatocellular tumours in one initiation–promotion study in rats, and in one initiation–promotion study in mice.

Kanechlor 500 was tested for carcinogenicity in one feeding study in male mice, one feeding study in male and female mice, and one initiation–promotion study of transplacental/perinatal exposure in male and female rats. It was also tested in three initiation–promotion studies, one in rats and two in mice, examining promoting activity. Kanechlor 500 caused significant increases in the incidence of hepatocellular carcinoma in both studies of carcinogenicity in male and female mice. Transplacental/perinatal administration of Kanechlor 500 decreased the incidence of NDEA-initiated tumours of the liver in rats. Kanechlor 500 promoted hepatocellular tumours in the three initiation–promotion studies.

5.4 Mechanistic and other relevant data

5.4.1 Absorption, distribution, metabolism, and elimination

(a) Absorption

In humans, gastrointestinal absorption of PCBs was estimated to vary from 50% of the ingested amount to close to 100%, the absorption decreasing as the number of chlorine atoms of the congener increased. A similar situation was observed in experimental animals. Although no quantitative data were available regarding absorption of PCBs in humans exposed by inhalation, the levels of residues detected in individuals exposed to high concentrations of PCBs in air suggested that inhaled PCBs are absorbed to a substantial extent. Data from experimental animals indicated that inhalation of PCBs gives a higher uptake of PCBs than ingestion. Studies assessing dermal exposure to commercial PCB mixtures in humans and animals showed that this route of exposure generally results in absorption levels of between 20% and 40%, with dermal penetration varying inversely with the degree of chlorination of the mixture administered. First-pass metabolism at the site of dermal exposure appears to be responsible for differences in metabolism and disposition between routes of administration. The rate of absorption and the disposition of PCBs after dermal administration may be mediated by transdermal metabolism.

(b) Distribution

PCBs are lipophilic compounds that are preferentially retained and may accumulate in adipose tissue and lipid-rich tissues. A few studies mentioned substantial retention of certain congeners in the lung and spleen in mice and rats, respectively. The pattern of congeners observed in tissues of humans or experimental animals does not correspond to the congener profiles of PCB formulations. The major PCB components in the plasma and adipose tissue of occupationally exposed individuals are the hexa- and heptachlorobiphenyls. PCB congeners with chlorine atoms in the *para* positions are generally found at relatively high concentrations, while PCBs with unsubstituted *meta*,*para* positions on at least one ring are present at lower concentrations. The most abundant congeners found in adipose tissue, plasma, and liver are 2,2′,3,4,4′,5′-hexachlorobiphenyl (PCB-138), 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) and 2,2′,3,4,4′,5,5′-heptachlorobiphenyl (PCB-180). PCBs have been found to cross the blood–brain barrier, and data from humans and experimental animals provided clear evidence for the transplacental passage of these chemicals. Metabolites of PCBs, including hydroxylated PCBs and methylsulfone PCBs, are also known to distribute to various tissues.

(c) Metabolism

Individual PCB congeners differ greatly in the ease with which they are metabolized in humans and animals. Congeners with four or fewer chlorines and those with adjacent unsubstituted *meta*,*para* positions are metabolized more readily than those with more than four chlorines and with substituents at *meta*,*para* ring positions. The initial step in the biotransformation of all PCB congeners is cytochrome P450 (CYP)-dependent mono-oxygenation. Readily metabolized congeners can be converted to potentially electrophilic and genotoxic metabolites of PCBs, arene oxides, and quinones. Quinones arise from dihydroxylated PCB metabolites through the action of peroxidases or prostaglandin endoperoxide synthase. The other major pathway of metabolism of PCBs is conversion of an arene oxide metabolite to a glutathione conjugate. The glutathione conjugate is then converted either to the excreted non-toxic mercapturic acid, or to the generally poorly excreted methyl sulfone metabolite.

(d) Elimination

Highly chlorinated congeners persist in the body, with half-lives averaging about 8–15 years; the half-lives of less chlorinated PCBs are distinctly shorter. In addition, PCB half-lives vary according to species, being longer in humans than in experimental animals, including monkeys. PCBs are mainly excreted via the faeces, while urine usually represents a minor route of excretion. Faecal excretion concerns not only unabsorbed PCBs, but also the excretion of biliary metabolites in the intestine. The proportion as well as the rate of elimination in the excreta depends on the type of mixture or congener and the route of exposure. Excretion profiles, and metabolite profiles in excreta, were different after administration of a dermal dose of PCBs when compared with an equivalent intravenous dose.

In addition to hydroxylated and dihydroxylated PCBs, the corresponding glucuronide and sulfate conjugates, as well as mercapturic acids, have also been characterized in the urine. Lactation is also a major route of excretion of PCBs in animals and humans. Minor routes of excretion such as elimination through the intestinal wall in the gastrointestinal tract or via the skin may also occur.

5.4.2 Genetic and related effects

A very limited number of studies in humans was available on cytogenetic effects in peripheral lymphocytes (chromosomal aberration, sister-chromatid exchange, micronucleus formation) and urinary concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in populations with possible exposure to PCBs. Although all these studies provided valuable information on genetic and related effects in humans exposed occupationally and environmentally to PCBs, the interpretation and generalization of the results was hindered by lack of information about PCB exposure, analysis, and levels, the lack of a real unexposed control population, the small number of individuals examined, confounding exposure to other chemicals, and lifestyle factors.

Several reports of sperm DNA damage and chromosome aneuploidy indicated that the testis may be a target organ for toxicity associated with PCBs.

Some very recent studies indicated that PCBs affect DNA methylation patterns in exposed humans, with long-term consequences for gene expression and chromosome stability. Since genes encoding for steroid hormone-synthesizing enzymes and oncogenes have been shown to be targeted, this may have significant implications for a possible mode of action of carcinogenesis by PCBs.

There was a lack of data about levels or even occurrence of individual PCB congeners in publications on the genotoxic effects of PCBs in humans. Only a few recent studies had analysed a very small number of congeners and calculated correlations with biological effects. Statistically positive correlations were found between serum concentration of PCB-118 and formation of micronuclei and DNA strand breaks (comet assay) in peripheral lymphocytes, serum concentrations of PCB-153 and DNA fragmentation in sperm, serum concentrations of PCB-138 and PCB-153 and *KRAS* mutation in tumours of the pancreas and brain, and PCB-95 concentrations and autism with a genetic basis (maternal dup15q11–q13 and Prader-Willi syndrome). These were interesting observations, but not sufficient to allow a structure–activity correlation.

Of all the commercial PCB mixtures, Aroclor 1254 has been by far the most extensively investigated for genetic effects in vitro and in vivo. Although numerous studies in vitro and in vivo with a negative outcome have been reported, almost none are suitable for hazard assessment, primarily due to the low doses tested and, in case of studies in vitro, the lack of an exogenous metabolic system. Thus the Working Group concluded, on the basis of a positive test for cell transformation and a weakly positive study of mutagenicity in transgenic mice in vivo, that mutagenicity associated with long-term exposure to Aroclor 1254 cannot be excluded with certainty.

Studies of mutagenicity with individual PCBs were available for 13 congeners. The most frequently investigated congener was monochlorinated PCB-3 and its metabolites, and studies in vitro and in vivo provided clear evidence that PCB-3 causes mutation in vitro and in vivo. However, metabolic activation to electrophilic species, i.e. quinones, is required, as shown by direct testing of PCB-3 metabolites for gene mutagenicity in vitro. The experimental evidence overall suggested that both DNA-adduct formation and generation of reactive oxygen species must be considered equally plausible modes of action.

Since both in-vitro and in-vivo studies provided evidence that PCB congeners with up to four chlorines are metabolically activated to electrophilic species that cause an increase in DNA-adduct levels, it seems likely that PCBs with one to four chlorines have the same mode of action as PCB-3. In contrast, strong evidence suggested that decachlorinated PCB-209 is very unlikely to cause mutations.

For dioxin-like PCB-126, a dose-dependent increase in DNA-adduct formation – resulting from lipid peroxidation or oxidative damage of the DNA backbone – has been reported in rats exposed to PCB-126 in the long-term. Thus, a genotoxic mechanism, probably via generation of reactive oxygen species, seems to contribute to the mode of action of PCB-126.

For non-dioxin-like PCB-153, a complete lack of genotoxic activity cannot be established with certainty since three in-vitro studies gave positive results. However, mechanistic follow-up studies in vitro and/or in vivo were not available to the Working Group. Thus, the relevance of this finding remains elusive.

For all other nine PCB congeners tested, i.e. PCB-15, PCB-47, PCB-52, PCB-77, PCB-101, PCB-118, PCB-138, PCB-155, and PCB-180, the Working Group considered that the results did not allow a clear conclusion to be drawn.

5.4.3 Cellular and biochemical effects

PCB congeners can be categorized according to their degree of chlorination, substitution pattern, and binding affinity to receptors. Individual PCB congeners activate receptors, including the aryl hydrocarbon, constitutive androstane, and pregnane xenobiotic receptors, and modulate gene expression controlled by these receptors/transcription factors.

(a) Cell death and proliferation

Twelve PCB congeners that have a strong affinity for the aryl hydrocarbon receptor are referred to as "dioxin-like PCBs." Activation of the aryl hydrocarbon receptor is one of the key events linked to carcinogenesis mediated by dioxin-like compounds. Besides its role in induction of CYP1 enzymes (linked to toxicity and cancer initiation), sustained activation leads to deregulation of cell-cycle control and cell proliferation, inhibition of apoptosis, suppression of cell–cell communication and adhesion, and increased cell plasticity and invasiveness. In accordance with the concept of toxic equivalency, PCB-126 is the most potent aryl-hydrocarbon receptor agonist of the PCBs, followed by PCB-169; mono-*ortho* chlorinated PCBs (e.g. PCB-118, PCB-156), and PCB-77 also activate the aryl hydrocarbon receptor, although to a lesser extent.

On the other hand, non-dioxin-like PCBs induce many of their effects via multiple aryl hydrocarbon receptor-independent mechanisms, including activation of the constitutive androstane or pregnane X receptors, and perturbations in cell–cell communication and cell adhesion. Non-dioxin-like PCBs induce production of reactive oxygen species, activation of NF-κB transcription factors, and suppression of plasma membrane proteins, constituents of gap, adherens, and tight junctions, all of which may play a significant role in tumour promotion and progression. A series of non-dioxin-like PCBs, including less chlorinated congeners (e.g. PCB-18, PCB-47, PCB-52, and PCB-74), environmentally abundant congeners (e.g. PCB-138 and PCB-153), and hydroxylated metabolites, such as 3′,4′-di(OH)PCB-5, 4-OH-PCB-109 (4-OH-2,3,3′,4′,5-pentaCB), and 4-OH-PCB-187, inhibited gap junction intercellular communication in rat liver epithelial cells. A mixture of seven non-dioxin-like PCBs (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180, and PCB-209) induced production of reactive oxygen species and cell motility in human breast cancer cells. Both the dioxin-like congener PCB-126, and the non-dioxin-like congeners PCB-118 and PCB-153 disrupted the expression of cytosolic scaffold proteins of tight junctions in brain endothelial cells in mice. Expression of anti-apoptotic *Bcl2* gene in a short-term study in female rat liver, to decrease apoptotic index and to suppress the levels of gap junction and adherens junction proteins (connexin 43, β-catenin, E-cadherin) in rat liver epithelial cells. PCB-28, PCB-101, PCB-153, and also PCB-187 (to a lesser

extent) suppressed apoptosis in rat hepatocytes and human hepatoma HepG2 cells.

(b) Endocrine disruption

Population-based studies in men and women have shown an inverse correlation between serum concentrations of PCBs and circulating testosterone, including testosterone bound to sex-hormone-binding globulin. Studies on mother–infant pairs showed an inverse relationship between indicator PCBs and testosterone in female infants, which was statistically significant with the mono-*ortho* congeners PCB-105 and PCB-118, while male infants showed a stronger reduction in estradiol with higher serum concentrations of PCBs.

In studies on extracts of PCBs from human serum, higher serum PCB concentrations correlated with lower activities of the estrogen, androgen, and aryl hydrocarbon receptors.

The observed inverse trend between dioxin-like PCBs and activities of the aryl hydrocarbon and estrogen receptors suggests that these compounds have anti-estrogenic activity. In cultured cells, highly chlorinated congeners generally act as anti-estrogens and their hydroxylated metabolites are more active than the parent compound. In contrast, less chlorinated PCBs and their hydroxylated metabolites are generally estrogenic, and their potency is dependent upon *ortho* chlorination and *para* hydroxylation; estrogenic activities of the hydroxylated metabolites of less chlorinated PCBs were reported to be additive.

Studies with cultured cells demonstrated that some PCBs are androgen-receptor antagonists, the anti-androgenic effects of dioxin-like PCBs being more pronounced than those of *ortho*-substituted PCBs. This antagonism has been associated in humans with several factors related to an increased risk of cancer of the testis.

In population-based studies, an inverse correlation was also reported between total serum PCBs and triiodothyronine, thyroxine, and thyroid-stimulating hormone. For hydroxylated PCBs, a positive correlation was found with free thyroxin in umbilical cord tissue of fetuses after in-utero exposure.

Studies in rats demonstrated that hydroxylated PCBs that bind to the thyroid receptor act as agonists to the thyroid hormone; one metabolite even displayed a higher binding affinity than does thyroxine, the natural ligand. PCBs with chlorines in the *ortho* position only have significant binding affinity for the transport protein transthyretin.

Hydroxylated PCBs may cross the placental barrier, probably through binding to transthyretin, thus causing a reduction of total and free thyroxine concentrations in fetal plasma and brain. Moreover, pre- and postnatal exposure to PCBs and their hydroxylated metabolites can interfere with the thyroid-hormone system, which may lead to a decrease in levels of thyroid hormone.

Disturbance of thyroxine-binding to transthyretin by PCB metabolites and increased glucuronidation causes a reduction in serum thyroxine concentrations in Aroclor 1254-exposed rats. The interference of PCBs with the thyroid system in vitro as well as in animals corroborates the effects observed in human population studies. The effects of PCBs on thyroid-hormone function, metabolism and transport may increase the risk for toxicity and pre-cancerous processes.

In a study that considered 10 different mechanisms to establish in-vitro toxicity profiles for 24 PCB congeners, hierarchical cluster analysis showed that 7 indicator PCBs contributed most to the anti-androgenic, (anti)estrogenic, and anti-thyroidal effects of PCBs reported to be present in human samples.

(c) Effects on the immune system

The limited data available for human exposure suggested that PCBs may cause immunosuppression. PCBs can affect an impressive number of immune parameters that include

changes in bone-marrow cellularity; shifts in T-lymphocyte subsets and function; thymus and spleen atrophy, which correlate strongly with humoral and cell-mediated immunosuppression; reduced resistance to microbial infection; and a compromised immune-surveillance mechanism. Alterations in the immune system and immunotoxicity were also reported after PCB exposure during prenatal or early life.

An estimation of the degree of immunotoxicity induced by various PCB congeners and mixtures is hindered by the fact that several species with significant differences in sensitivity were used across the studies, with different routes of exposure and levels of treatment. In general, doses of > 1 mg/kg bw per day of the highly chlorinated commercial PCB mixtures (Aroclors 1248, 1254, 1262, and 1260) were more immunotoxic than the less chlorinated PCB mixtures. The few individual congeners tested in rats caused only minor changes in the thymus without affecting other parameters of the immune system.

Non-human primates are more sensitive to PCB-induced immunotoxicity. In long-term studies in rhesus monkeys exposed at levels similar to those in humans, a consistent finding was the significantly suppressed response to challenge with sheep red blood cell antigen in adult and infant monkeys. Similar results were observed in many other experimental animals at higher concentrations of PCBs.

The humoral immune response to sheep red blood cell antigen is the most predictive of the tests currently used in immunotoxicology, and has been used in the calculation of TEFs. The TEF calculation is based on the assumptions that the effects of PCBs on the immune system are mediated through the aryl hydrocarbon receptor, and that PCBs in mixtures may have an additive effect. Nonetheless, certain PCBs exert their immunotoxic effects by mechanisms that are not mediated through the aryl hydrocarbon receptor; such effects are thought to be mediated via metabolism to arene-oxide intermediates capable of alkylating critical cellular macromolecules. Additionally, certain non-dioxin-like PCBs may antagonize the immunotoxic effects of other chemicals, including those of dioxin.

The effects on the immune system were shown to persist in children at a later age. The severity of effects correlated with PCB concentrations in the children's blood, or with those in maternal blood during pregnancy and lactation. Similar results were obtained in experimental animals.

(d) Effects on the inflammatory response

Exposure to PCBs has been associated with the development of inflammation in several studies in experimental animals in vivo; chronic active inflammation can be detected specifically in tissues that are affected by PCB exposure.

In in-vivo studies in mice, it has been reported that PCB-77, PCB-104, and PCB-153 are associated with inflammation in target organs since they induced the production of specific inflammatory mediators, including intercellular adhesion molecules (e.g. ICAM, VCAM-1, MCP-1) in the liver, lungs, and brain. The tissue distribution of these inflammatory mediators varied according to the congener administered, probably due to differences in congener accumulation in the various organs.

PCBs have also been shown to cause vascular inflammation in vivo.

In vitro, PCB-153 may induce expression of several pro-inflammatory cytokines through NF-κB pathway inhibitor.

Several PCB congeners and mixtures, including Aroclor 1242 and PCB-47, interfere with O_2^- elimination by suppressing the activity of superoxide dismutase which converts O_2^- to H_2O_2. Non-dioxin-like PCBs are capable of stimulating neutrophil O_2^- production, while dioxin-like congeners with a high affinity for the aryl hydrocarbon receptor do not activate neutrophils to produce O_2^- and may inhibit this response.

Certain congeners (PCB-77, PCB-114, PCB-126, and PCB-169) disrupted the normal functions of the vascular endothelium, thus allowing increased transfer of albumin across endothelial monolayers. The same congeners enhanced oxidative stress, increased production of interleukin-6 by endothelial cells, increased the levels of intracellular calcium, increased the activity of cytochrome P450 1A, enhanced expression of the adhesion molecule VCAM-1, and decreased levels of vitamin E in the culture medium. In contrast, PCB-153 did not have an effect on cellular oxidation or on endothelial barrier function.

5.4.4 Classification of congeners and quantitative structure–activity relationships

Different key structural determinants of the toxicity of individual PCB congeners were identified in various in-vitro assays for specific effects of tumour promotion, endocrine disruption, and neurotoxicity. Multivariate toxicity profiling of a series of PCB congeners indicated that many of the responses are due to different structure–activity relationships and cannot be integrated. The use of quantitative structure–activity relationships is also hampered at present by the lack of data on specific cancer-related modes of action for larger sets of congeners.

5.4.5 Hepatic preneoplastic lesions

Numerous studies have used preneoplastic lesions as end-points to study the effects of PCBs on two-stage hepatocarcinogenesis. PCBs have promoting activity, especially congeners and mixtures that activate the aryl hydrocarbon and/or constitutive androstane receptors. When non-*ortho* and di-*ortho* PCBs are coadministered, less than additive effects are observed in most studies, while administration of two non-*ortho* PCBs is additive. Several less chlorinated PCBs have initiating activity.

5.4.6 Organ toxicity

Organ toxicity relevant to the carcinogenicity of long-term exposure to PCB congeners and commercial mixtures of PCBs in experimental systems is observed in the liver and also in other organs, notably the lung and thyroid.

5.4.7 Effects on skin

Chloracne and other dermal alterations are well-known effects that have been reported in workers exposed occupationally to PCBs, and in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs (Yusho and Yucheng victims). Chloracne generally appears in individuals with serum PCB concentrations that are 10–20 times higher than those of the general population, but there is large variability between individuals. At birth, children exposed in utero during food poisoning incidents had increased rates of hyperpigmentation, eyelid swelling and discharge, deformed nails, and acne, compared with controls.

Long-term oral administration of relatively low doses of PCBs to rhesus monkeys resulted in dermal alterations similar to those observed in humans exposed at high concentrations. Offspring from monkeys exposed during gestation and nursed by exposed mothers also developed dermal alterations after a few weeks of suckling. Rodents also develop skin alterations, but only after high exposures to PCBs.

Exposure of normal human melanocytes to TCDD resulted in activation of the aryl hydrocarbon receptor signalling pathway, an aryl hydrocarbon receptor-dependent induction of tyrosinase and – as a consequence – an elevated total melanin content. These effects were due to the induction of expression of tyrosinase and tyrosinase-related protein 2 genes. Thus, the

aryl hydrocarbon receptor is able to modulate melanogenesis by controlling the expression of melanogenic genes. This lends biological plausibility to the epidemiological findings of increased risks of melanoma of the skin after exposure to PCBs.

5.4.8 Susceptible populations

(a) Genetic polymorphisms

Differences in response to individual congeners may arise from polymorphisms in the genes for CYP, the aryl hydrocarbon receptor and repressor, and other enzymes and receptors that interact with endogenous molecules such as steroid hormone receptors. Studies in the most highly exposed populations reported a higher incidence of cancer of the breast in women with the *CYP1A1*2C* genotype; of non-Hodgkin lymphoma and a polymorphism in the gene encoding the aryl hydrocarbon receptor; and of skin lesions in Yucheng victims who had the *CYP1A1*2C* polymorphism and were null for *GSTM1*.

(b) In-utero and postnatal exposure

PCBs can pass through the placenta during embryonic development and is excreted in breast milk. In addition, compared with adults, children have a lower barrier to absorption through the skin, gastrointestinal tract, and lungs, and lower levels of detoxifying enzymes. A combination of all these factors leads to a higher accumulation of PCBs in children. The determination of PCB concentrations in cord blood, breast milk, and in tissues of mother/infant have contributed significantly to the understanding of the movement of these compounds from mother to infant and their distribution patterns throughout the body.

A significant dose-dependent relationship exists between the duration of breastfeeding and the concentration of the sum of congeners PCB-101, PCB-118, PCB-138, PCB-153, PCB-170, PCB-180, PCB-183, and PCB-187. Exclusive breastfeeding beyond 12 weeks was associated with a doubling in the whole blood concentration of PCBs compared with bottle-fed children.

Elimination kinetic studies in children with elevated PCB concentrations as a result of breastfeeding revealed differences in congener half-lives. The longest half-lives corresponded to elimination of the parent PCB only, with a daily fat excretion rate of 1–2 g, while shorter half-lives were attributable to metabolic breakdown.

Long-term studies in non-human primates receiving Aroclor 1254 have shown that in tissues of mother/infants with higher concentrations of PCBs, a dramatic shift from tetra- and hexachlorobiphenyls to penta-and heptachlorobiphenyls was observed. The PCB distribution pattern in tissues from a dosed mother/infant pair differed between mother and infant, with a larger percentage of heptachlorobiphenyls in the infant than in its dam. PCB concentrations in the infant's blood declined rapidly and approached maternal levels within 40–50 weeks; at 100 weeks after weaning, PCB concentrations in the adipose tissue of exposed infants were similar to background levels found in the control group.

Tissue retention/accumulation of PCBs in postnatal and prepubertal studies in mice showed results consistent with the well known effect of chlorine-substitution pattern on the rate of metabolism. In the lung, all congeners except PCB-153 were retained and decreased in amount only as a function of dilution due to growth. The selective retention of congeners with high affinity for the aryl hydrogen receptor is of interest since it is a property that correlates with toxicity and tumour promotion. In the liver, retention of all congeners was observed during the prepubertal growth phase, with specific enrichment of PCB-105, followed subsequently by more rapid depletion of certain congeners.

Prenatal/postnatal (through breastfeeding) exposure to PCBs can affect the dynamics of cell-surface receptor expression on lymphoid cells. These effects result in dysfunctional

immune responses, which may have adverse immune-system related consequences on the health of infants and toddlers. Furthermore, PCB-induced effects on the thymus and natural killer cells have been reported in children, and these effects may play a role in the development of leukaemia in these children.

5.4.9 Mechanistic considerations

PCBs and their metabolites have multiple modes of action. Less chlorinated congeners involved in oxidative metabolism may produce oxidative stress and genotoxicity; highly chlorinated congeners are very persistent and interact with various receptors including the aryl hydrocarbon, constitutive androstane, pregnane-X (controlling xenobiotic and steroid hormone metabolism and other processes), and steroid nuclear receptors such as the androgen and estrogen receptors. Additionally, PCBs modulate plasma membrane-associated proteins affecting cell communication, adhesion and migration, and also act as tumour promoters. Overall, PCBs occur and act in complex mixtures eliciting both genotoxic and nongenotoxic effects associated with carcinogenesis, tumour promotion, and progression.

6. EVALUATION AND RATIONALE

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of polychlorinated biphenyls (PCBs). PCBs cause malignant melanoma. Positive associations have been observed for non-Hodgkin lymphoma and cancer of the breast.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of PCBs.

There is *sufficient evidence* in experimental animals for the carcinogenicity of PCB-126, PCB-118, Aroclor 1260, Aroclor 1254, and Kanechlor 500.

There is *limited evidence* in experimental animals for the carcinogenicity of PCB-153, 4′-OH-PCB-30, 4′OH-PCB-61, Aroclor 1242, Aroclor 1016, Clophen A30, and Clophen A60.

There is *inadequate evidence* in experimental animals for the carcinogenicity of PCB-138, Kanechlor 300, and Kanechlor 400.

Congeners for which there is *sufficient evidence* in experimental animals for carcinogenicity (PCB-126 and PCB-118) are agonists of the aryl hydrocarbon receptor and exhibit dioxin-like properties. Commercial mixtures for which there is *sufficient evidence* in experimental animals for carcinogenicity are highly chlorinated and are known to include aryl-hydrocarbon receptor agonists that exhibit dioxin-like properties, as well as agonists of the constitutive androstane receptor.

The commercial mixtures for which there is *limited evidence* in experimental animals generally have a low degree of chlorination, but are also known to contain congeners that are agonists of the aryl hydrocarbon and/or constitutive androstane receptors. The relative contributions of the different congeners (dioxin-like and non-dioxin-like) to the carcinogenicity of the commercial mixtures is not known.

6.3 Overall evaluation

PCBs are *carcinogenic to humans (Group 1).*

"Dioxin-like" PCBs, with a toxicity equivalency factor (TEF) according to WHO (PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-169, PCB-156, PCB-157, PCB-167, PCB-189), are *carcinogenic to humans (Group 1).*

6.4 Rationale

In making this overall evaluation, the Working Group considered that:

- There is strong evidence to support a receptor-mediated mechanism for carcinogenesis associated with dioxin-like PCBs in humans, based upon demonstration of carcinogenicity in experimental animals and upon extensive proof of activity identical to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) for every step of the mechanism described for

TCDD-associated carcinogenesis in humans, including receptor binding, gene expression, protein-activity changes, cellular replication, oxidative stress, promotion in initiation–promotion studies and complete carcinogenesis in experimental animals.

- However, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs.

POLYBROMINATED BIPHENYLS

POLYBROMINATED BIPHENYLS

1. Exposure Data

1.1 Identification of the agents

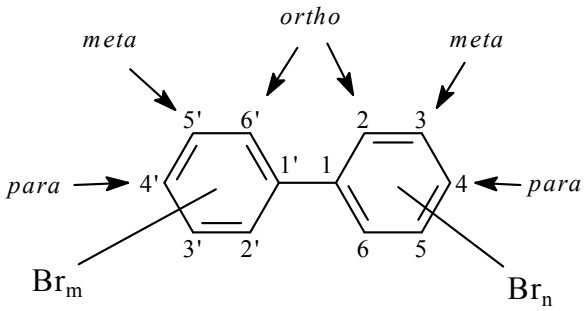
The terms "polybrominated biphenyls" or "polybromobiphenyls" (PBBs) refer to a group of halogenated hydrocarbons that are formed by substituting hydrogen with bromine on a biphenyl ring. PBBs have a molecular formula of $C_{12}H_{(10-n-m)}Br_{(n+m)}$ where n + m = 1 to 10, i.e. from monobromobiphenyl to decabromobiphenyl.

There are 209 possible structural congeners of the brominated biphenyl structure containing one or more bromines; however, only a few of these have been synthesized individually and characterized (Stepniczka, 1976; Sundström *et al.*, 1976a). The number of PBB congeners that actually exist in commercial mixtures is much lower than that of polychlorinated biphenyls (PCB) congeners.

Like for PCBs, positions 2, 2′, 6, and 6′ are called *ortho* positions, positions 3, 3′, 5, and 5′ are called *meta* positions, and positions 4 and 4′ are called *para* positions (Fig. 1.1).

The benzene rings can rotate around the 1,1′ carbon bond. The two theoretical extreme configurations are planar (angle = 0°) and perpendicular (the two benzene rings are in perpendicular planes). The degree of planarity is largely determined by the number of substitutions in the *ortho* positions. Since bromine atoms are more bulky than chlorine atoms, substitution in *ortho* positions for PBBs is much less favoured than for PCBs. The replacement of hydrogen atoms in the *ortho* positions with bromine atoms forces the benzene rings to adopt a configuration with a larger angle. The benzene rings of non-*ortho* as well as mono-*ortho* substituted PBBs adopt a small angle so that the configuration is nearly planar (Fig. 1.2).

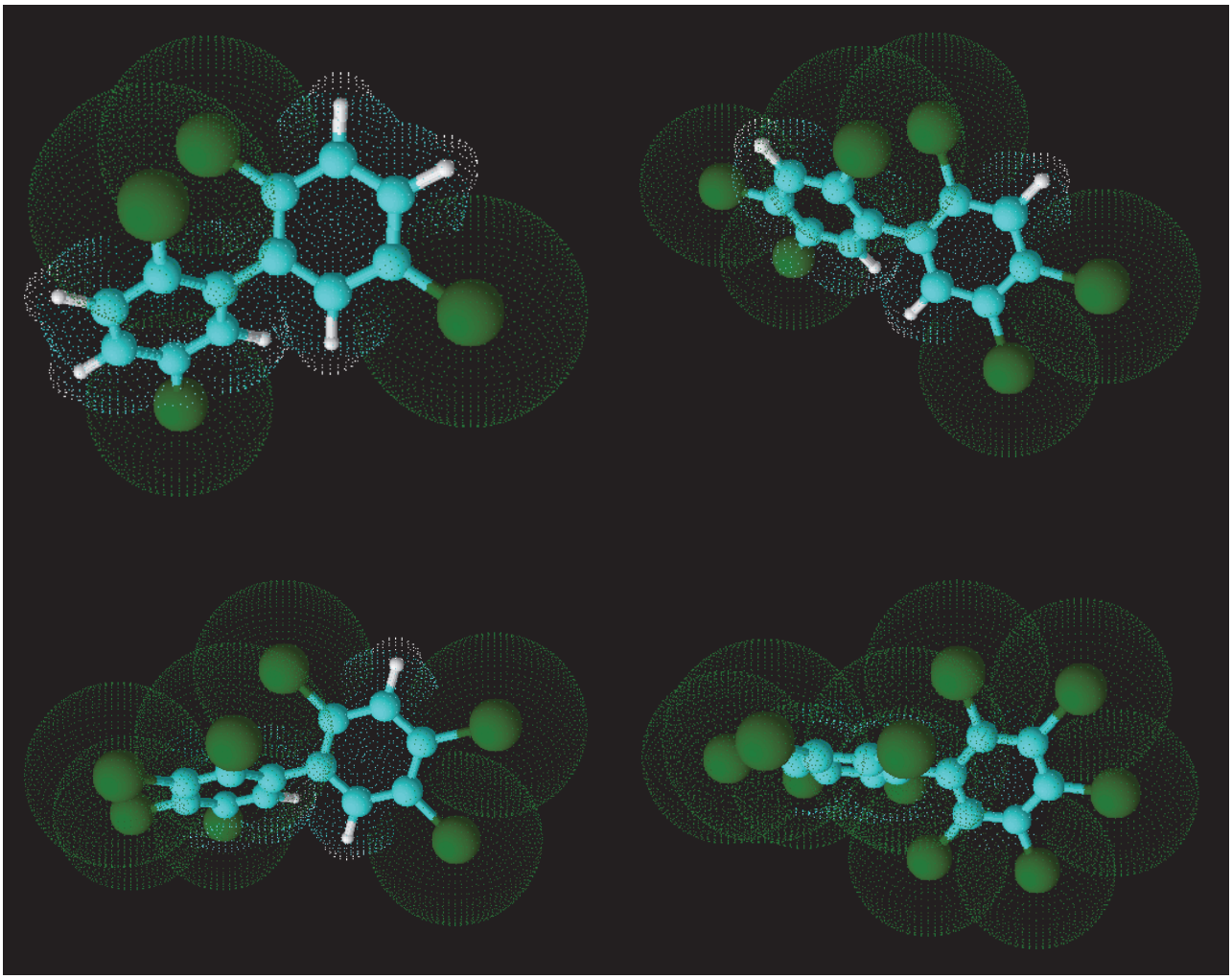
Fig. 1.1 Chemical structure of polybrominated biphenyls and the IUPAC numbering system



Hydrogen atoms in positions 2,2′,6,6′ (*ortho*), 3,3′,5,5′ (*meta*) and/or 4,4′ (*para*) may be substituted by bromine atoms; n+m = 1–10
IUPAC, International Union of Pure and Applied Chemistry
Compiled by the Working Group

The numbering of PBBs from 1 to 209 corresponds to the scheme developed for PCBs by Ballschmiter & Zell (1980) and updated in Ballschmiter *et al.* (1992), i.e. in ascending numerical order, which generally follows the rules of the International Union of Pure and Applied Chemistry (IUPAC) for substituent characterization of biphenyls (rule A-52.3 related to hydrocarbon systems) (Table 1.1). This numbering system, referred to as BZ numbering, is widely used for identifying

Fig. 1.2 Tridimensional chemical structures of PBBs



Spatial configurations of three mono-*ortho* PBBs, e.g. PBB-52 (2,2′,5,5′-tetraBB, up and left), PBB-153 (2,2′,4,4′,5,5′-hexaBB, up and right), and PBB-180 (2,2′,3,4,4′,5,5′-heptaBB, down and left), and non-coplanar configuration of one di-*ortho* PBB, e.g. PBB-209 (2,2′,3,3′,4,4′,5,5′,6,6′-decaBB, down and right)
BB, brominated biphenyl; PBBs, polybrominated biphenyls
Courtesy of Professor B. LeBizec

Table 1.1 BZ number and correspondence between the positions of bromine atoms on each phenyl ring of the PBBs (nomenclature according to Ballschmiter *et al.*, 1992)[a]

Position of bromine atom on each ring	2	3	4	2,3	2,4	2,5	2,6	3,4	3,5	2,3,4	2,3,5	2,3,6	2,4,5	2,4,6	3,4,5	2,3,4,5	2,3,4,6	2,3,5,6	2,3,4,5,6
None	1	2	3	5	7	9	10	12	14	21	23	24	29	30	38	61	62	65	116
2′	4	6	8	16	17	18	19	33	34	41	43	45	48	50	76	86	88	93	142
3′		11	13	20	25	26	27	35	36	55	57	59	67	69	78	106	108	112	160
4′			15	22	28	31	32	37	39	60	63	64	74	75	81	114	115	117	166
2′,3′				40	42	44	46	56	58	82	83	84	97	98	122	129	131	134	173
2′,4′					47	49	51	66	68	85	90	91	99	100	123	137	139	147	181
2′,5′						52	53	70	72	87	92	95	101	103	124	141	144	151	185
2′,6′							54	71	73	89	94	96	102	104	125	143	145	152	186
3′,4′								77	79	105	109	110	118	119	126	156	158	163	190
3′,5′									80	107	111	113	120	121	127	159	161	165	192
2′,3′,4′										128	130	132	138	140	157	170	171	177	195
2′,3′,5′											133	135	146	148	162	172	175	178	198
2′,3′,6′												136	149	150	164	174	176	179	200
2′,4′,5′													153	154	167	180	183	187	203
2′,4′,6′														155	168	182	184	188	204
3′,4′,5′															169	189	191	193	205
2′,3′,4′,5′																194	196	199	206
2′,3′,4′,6′																	197	201	207
2′,3′,5′,6′																		202	208
2′,3′,4′,5′,6′																			209

[a] Nomenclature of the PBBs follows that of polychlorinated biphenyls (PCBs). For several PBB congeners, the indicated structural names do not correspond strictly to the IUPAC rules (primed and unprimed numbers are interchanged). A comprehensive survey of PCB nomenclature, including IUPAC names, is given in Mills *et al.* (2007). This nomenclature includes revised numbering of congeners 107–109.

BZ, Ballschmiter & Zell; IUPAC, International Union of Pure and Applied Chemistry; PBBs, polybrominated biphenyls

individual congeners of PBBs. For example, the PBB congener 3,3′,4,4′,5,5′-hexabromobiphenyl is referred to as PBB-169. The relationship between PBB BZ number and Chemical Abstracts Service (CAS) number is given in Table 1.2.

PBBs can be categorized by degree of bromination, and compounds with the same number of bromines are called homologues. Based on the number of bromine substituents, there are 10 homologous groups of PBBs (monobromobiphenyls to decabromobiphenyls). The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 form(s), respectively (Table 1.3). Homologues with different patterns of substitution are referred to as isomers.

1.1.1 Chemical and physical properties of PBBs

The properties of congeners as reported by earlier investigators may be questionable due to insufficient purification of the congener. More accurate data on physical and chemical properties have been reported recently (Table 1.3; Tittlemier *et al.*, 2002). PBBs are chemically comparable to PCBs, with properties linked to bromine, which is a better leaving group in chemical reactions than chlorine. Pure single PBB compounds are mostly colourless or slightly yellowish, often odourless. The commercial products are typically white, off-white, or beige powdered solids (DiCarlo *et al.*, 1978; Tittlemier *et al.*, 2002). PBBs are characterized by low volatility (Table 1.3), which decreases with increasing bromine number (Farrell, 1980; NTP, 2011). PBBs with three or more bromines are solids (Sundström *et al.*, 1976a; de Kok *et al.*, 1977).

PBBs are nearly insoluble in water, and solubility decreases with increasing bromination. PBBs are soluble in fat (Kay, 1977) and slightly to highly soluble in various organic solvents. Partition ratios between 1-octanol and water (log K_{ow}) increase with the number of bromines (Table 1.3; IARC, 1986). Unlike PCBs, the reactivity of PBBs has not been well studied or documented in the literature. Henry's law constant for the hexabromobiphenyls ranges from 1.4×10^{-8} to 3.9×10^{-8} atm-m^3/mol.

Like PCBs, the chemical stability of PBBs is dependent, in part, on the degree and specific pattern of substitution (bromination). However, PBBs show unusual chemical stability and resistance to breakdown by acids, bases, and reducing and oxidizing agents (Pomerantz *et al.*, 1978). Several of the common isomers photodegrade with reductive debromination upon exposure to ultraviolet light (Sundström *et al.*, 1976a; Kay, 1977; Pomerantz *et al.*, 1978). All highly brominated PBB mixtures are known to debrominate rapidly upon ultraviolet irradiation (DiCarlo *et al.*, 1978). Investigations into the pyrolysis of Firemaster BP-6 in the absence of oxygen (600–900 °C) have shown that bromobenzenes and lower brominated biphenyls are formed, but no polybrominated furans. In contrast, pyrolysis in the presence of oxygen (700–900 °C) yielded some di- to heptabromodibenzofurans (O'Keefe, 1978).

1.1.2 Trade names and composition of commercial mixtures

PBB mixtures have been manufactured mainly as three homologue groups: hexabromobiphenyls, octabromobiphenyls, and decabromobiphenyls (Table 1.4; Neufeld *et al.*, 1977; ATSDR, 2004; NTP, 2011). All commercial PBB mixtures are relatively highly brominated, with bromine contents ranging from about 76% for hexabromobiphenyls to 81–85% for octa- to decabromobiphenyl mixtures (Brinkman & de Kok, 1980). Commercial PBB mixtures were produced primarily by Berk Corporation in the United Kingdom [e.g. Berkflam B-10, Flammex B-10 (decabromobiphenyls)], Chemische Fabrik Kalk [e.g. Bromkal 80–9D (nonabromobiphenyl)] and Ugine Kuhlmann [e.g. Adine 0102

Table 1.2 BZ number, bromine positions, and CAS number for individual PBBs (*n* = 209)

BZ No.	Bromine positions	CAS No.
1	2	2052-07-7
2	3	2113-57-7
3	4	92-66-0
4	2,2′	13029-09-9
5	2,3	115245-06-2
6	2,3′	49602-90-6
7	2,4	53592-10-2
8	2,4′	49602-91-7
9	2,5	57422-77-2
10	2,6	59080-32-9
11	3,3′	16400-51-4
12	3,4	60108-72-7
13	3,4′	57186-90-0
14	3,5	16372-96-6
15	4,4′	92-86-4
16	2,2′,3	
17	2,2′,4	
18	2,2′,5	59080-34-1
19	2,2′,6	
20	2,3,3′	
21	2,3,4	
22	2,3,4′	
23	2,3,5	
24	2,3,6	
25	2,3′,4	
26	2,3′,5	59080-35-2
27	2,3′,6	
28	2,4,4′	6430-90-6
29	2,4,5	115245-07-3
30	2,4,6	59080-33-0
31	2,4′,5	59080-36-3
32	2,4′,6	64258-03-3
33	2′,3,4	
34	2′,3,5	
35	3,3′,4	
36	3,3′,5	
37	3,4,4′	6683-35-8
38	3,4,5	115245-08-4
39	3,4′,5	72416-87-6
40	2,2′,3,3′	
41	2,2′,3,4	
42	2,2′,3,4′	
43	2,2′,3,5	
44	2,2′,3,5′	
45	2,2′,3,6	
46	2,2′,3,6′	
47	2,2′,4,4′	66115-57-9
48	2,2′,4,5	
49	2,2′,4,5′	60044-24-8
50	2,2′,4,6	
51	2,2′,4,6′	97038-95-4
52	2,2′,5,5′	59080-37-4
53	2,2′,5,6′	60044-25-9
54	2,2′,6,6′	97038-96-5
55	2,3,3′,4	97038-99-8
56	2,3,3′,4′	
57	2,3,3′,5	
58	2,3,3′,5′	
59	2,3,3′,6	
60	2,3,4,4′	
61	2,3,4,5	115245-09-5
62	2,3,4,6	115245-10-8
63	2,3,4′,5	
64	2,3,4′,6	
65	2,3,5,6	
66	2,3′,4,4′	84303-45-7
67	2,3′,4,5	
68	2,3′,4,5′	
69	2,3′,4,6	
70	2,3′,4′,5	59080-38-5
71	2,3′,4′,6	
72	2,3′,5,5′	
73	2,3′,5′,6	
74	2,4,4′,5	
75	2,4,4′,6	64258-02-2
76	2′,3,4,5	
77	3,3′,4,4′	77102-82-0
78	3,3′,4,5	
79	3,3′,4,5′	97038-98-7
80	3,3′,5,5′	16400-50-3
81	3,4,4′,5	59589-92-3
82	2,2′,3,3′,4	
83	2,2′,3,3′,5	
84	2,2′,3,3′,6	
85	2,2′,3,4,4′	
86	2,2′,3,4,5	
87	2,2′,3,4,5′	
88	2,2′,3,4,6	77910-04-4
89	2,2′,3,4,6′	
90	2,2′,3,4′,5	
91	2,2′,3,4′,6	
92	2,2′,3,5,5′	

Table 1.2 (continued)

BZ No.	Bromine positions	CAS No.
93	2,2′,3,5,6	
94	2,2′,3,5,6′	
95	2,2′,3,5′,6	88700-05-4
96	2,2′,3,6,6′	
97	2,2′,3′,4,5	
98	2,2′,3′,4,6	
99	2,2′,4,4′,5	81397-99-1
100	2,2′,4,4′,6	97038-97-6
101	2,2′,4,5,5′	67888-96-4
102	2,2′,4,5,6′	80274-92-6
103	2,2′,4,5′,6	59080-39-6
104	2,2′,4,6,6′	97063-75-7
105	2,3,3′,4,4′	
106	2,3,3′,4,5	
107	2,3,3′,4,5′	
108	2,3,3′,4,6	
109	2,3,3′,4′,5	
110	2,3,3′,4′,6	
111	2,3,3′,5,5′	
112	2,3,3′,5,6	
113	2,3,3′,5′,6	
114	2,3,4,4′,5	96551-70-1
115	2,3,4,4′,6	
116	2,3,4,5,6	38421-62-4
117	2,3,4′,5,6	
118	2,3′,4,4′,5	67888-97-5
119	2,3′,4,4′,6	86029-64-3
120	2,3′,4,5,5′	80407-70-1
121	2,3′,4,5′,6	
122	2′,3,3′,4,5	
123	2′,3,4,4′,5	74114-77-5
124	2′,3,4,5,5′	
125	2′,3,4,5,6′	
126	3,3′,4,4′,5	84303-46-8
127	3,3′,4,5,5′	81902-33-2
128	2,2′,3,3′,4,4′	82865-89-2
129	2,2′,3,3′,4,5	
130	2,2′,3,3′,4,5′	82865-90-5
131	2,2′,3,3′,4,6	
132	2,2′3,3′,4,6′	119264-50-5
133	2,2′,3,3′,5,5′	55066-76-7
134	2,2′,3,3′,5,6	
135	2,2′3,3′,5,6′	119264-51-6
136	2,2′,3,3′,6,6′	
137	2,2′,3,4,4′,5	81381-52-4
138	2,2′,3,4,4′,5′	67888-98-6
139	2,2′,3,4,4′,6	
140	2,2′,3,4,4′,6	
141	2,2′,3,4,5,5′	120991-47-1
142	2,2′,3,4,5,6	
143	2,2′,3,4,5,6′	
144	2,2′,3,4,5′,6	119264-52-7
145	2,2′,3,4,6,6′	
146	2,2′,3,4′,5,5′	
147	2,2′,3,4′,5,6	
148	2,2′,3,4′,5,6′	
149	2,2′,3,4′,5′,6	69278-59-7
150	2,2′,3,4′,6,6′	93261-83-7
151	2,2′,3,5,5′,6	119264-53-8
152	2,2′,3,5,6,6′	
153	2,2′,4,4′,5,5′	59080-40-9
154	2,2′,4,4′,5,6′	36402-15-0
155	2,2′,4,4′,6,6′	59261-08-4
156	2,3,3′,4,4′,5	77607-09-1
157	2,3,3′,4,4′,5′	84303-47-9
158	2,3,3′,4,4′,6	
159	2,3,3′,4,5,5′	120991-48-2
160	2,3,3′,4,5,6	
161	2,3,3′,4,5′,6	
162	2,3,3′,4′,5,5′	
163	2,3,3′,4′,5,6	
164	2,3,3′,4′,5′,6	82865-91-6
165	2,3,3′,5,5′,6	
166	2,3,4,4′,5,6	
167	2,3′,4,4′,5,5′	67888-99-7
168	2,3′,4,4′,5′,6	84303-48-0
169	3,3′,4,4′,5,5′	60044-26-0
170	2,2′,3,3′,4,4′,5	69278-60-0
171	2,2′,3,3′,4,4′,6	
172	2,2′,3,3′,4,5,5′	82865-92-7
173	2,2′,3,3′,4,5,6	
174	2,2′,3,3′,4,5,6′	88700-04-3
175	2,2′,3,3′,4,5′,6	
176	2,2′,3,3′,4,6,6′	
177	2,2′,3,3′,4,5′,6′	
178	2,2′,3,3′,5,5′,6	119264-54-9
179	2,2′,3,3′,5,6,6′	
180	2,2′,3,4,4′,5′,6	67733-52-2
181	2,2′,3,4,4′,5,6	
182	2,2′,3,4,4′,5,6′	119264-54-9
183	2,2′,3,4,4′,5′,6	
184	2,2′,3,4,4′,6,6′	119264-56-1

Table 1.2 (continued)

BZ No.	Bromine positions	CAS No.
185	2,2′,3,4,5,5′,6	
186	2,2′,3,4,5,6,6′	119264-57-2
187	2,2′,3,4′,5,5′,6	84303-49-1
188	2,2′,3,4′,5,6,6′	119264-58-3
189	2,3,3′,4,4′,5,5′	88700-06-5
190	2,3,3′,4,4′,5,6	79682-25-0
191	2,3,3′,4,4′,5′,6	
192	2,3,3′,4,5,5′,6	
193	2,3,3′,4′,5,5′,6	
194	2,2′,3,3′,4,4′,5,5′	67889-00-3
195	2,2′,3,3′,4,4′,5,6	
196	2,2′,3,3′,4,4′,5′,6	
197	2,2′,3,3′,4,4′,6,6′	119264-59-4
198	2,2′,3,3′,4,5,5′,6	
199	2,2′,3,3′,4,5,5′,6′	
200	2,2′,3,3′,4,5,6,6′	119264-60-7
201	2,2′,3,3′,4′,5′,6,6′	69887-11-2
202	2,2′,3,3′,5,5′,6,6′	59080-41-0
203	2,2′,3,4,4′,5,5′,6	
204	2,2′,3,4,4′,5,6,6′	119264-61-8
205	2,3,3′,4,4′,5,5′,6	
206	2,2′,3,3′,4,4′,5,5′,6	69278-62-2
207	2,2′,3,3′,4,4′,5,6,6′	119264-62-9
208	2,2′,3,3′,4,5,5′,6,6′	119264-63-0
209	2,2′,3,3′,4,4′,5,5′,6,6′	13654-09-6

BZ, Ballschmiter & Zell; CAS, Chemical Abstracts Service Registry; PBBs, polybrominated biphenyls
From Ballschmiter & Zell (1980), Ballschmiter *et al.* (1992)

(decabromobiphenyl)] in Germany, and Michigan Chemical Corporation, White Chemical Corporation, and Hexcel Corporation in the USA [e.g. Firemaster BP-6 (CAS No. 59536-65-1) and FF-1 (CAS No. 67774-32-7)].

The exact composition of the mixtures varies between batches (see Section 1.3; Table 1.5) and also within each batch, according to sampling (see Section 1.2). The main constituents of Firemaster are hexabromobiphenyl (63–84%) and heptabromobiphenyl (12–25%), together with lesser brominated [pentabromobiphenyl (1–11%) and tetrabromobiphenyl (0–5%)] congeners (Sundström *et al.*, 1976b; DiCarlo *et al.*, 1978; Hass *et al.*, 1978; Robertson *et al.*, 1984a) due to incomplete bromination reactions (IPCS, 1994).

At least four ^{13}C-labelled PBB congeners are available commercially.

1.1.3 Contaminants and impurities of commercial mixtures of PBBs

Mixed polybromochlorobiphenyls (PXBs), e.g. monochloropentabromobiphenyl (CAS No. 88703-30-4), have been observed as minor contaminants in Firemaster (Tondeur *et al.*, 1984). Such compounds probably result from contamination of commercial bromine by chlorine (Domino & Domino, 1980). Contaminants of the initial biphenyl feedstock may ultimately appear in commercial mixtures of PBBs. Described impurities include toluene, naphthalene, methylene biphenyl (fluorene) and various methyl biphenyls (Neufeld *et al.*, 1977). It is assumed that naphthalene for instance, present as an impurity in industrial-grade biphenyl, is brominated during production, and that the presence of numerous isomers and congeners of polybrominated naphthalenes in the final product is possible (Robertson *et al.*, 1984a). Polybrominated benzenes and a possible methylbrominated furan have also been reported to occur in Firemaster(R) (Brinkman & de Kok, 1980). Polybromodibenzo-*p*-dioxins and polybromodibenzofurans were not detected above 0.5 mg/kg in the polar fraction of Firemaster FF-1 (Hass *et al.*, 1978). In another study, O'Keefe (1978) showed that polybrominated dibenzofurans were formed during pyrolysis of Firemaster FF-1. A sample of Adine 0102 (decabromobiphenyl) contained monobromobenzodifurans at 1 mg/kg and polybromodibenzodioxins and polybromodibenzofurans at below 0.01 mg/kg (IPCS, 1994). Although PBBs are relatively stable, highly brominated congeners are susceptible to photolytic debromination when they are exposed to ultraviolet light (see Section 1.1.1).

Table 1.3 Physical and chemical properties of homologue groups of PBBs

Homologue group	CAS No.	Formula	No. of isomers	BZ No.	Relative molecular mass	Melting point (°C)	Solubility (μg/L)	Volatility (Pa at 25 °C)[a] (calculated)[b]	Log K_{ow}[a]
Monobromobiphenyls	26264-10-8	$C_{12}H_9Br_1$	3	1–3	232.9				4.6 (PBB-1)
Dibromobiphenyls	27479-65-8	$C_{12}H_8Br_2$	12	4–15	311.8				
Tribromobiphenyls	51202-79-0	$C_{12}H_7Br_3$	24	16–39	390.7				
Tetrabromobiphenyls	40088-45-7	$C_{12}H_6Br_4$	42	40–81	469.6			5.0×10^{-4}	6.5 (PBB-52)
Pentabromobiphenyls	56307-79-0	$C_{12}H_5Br_5$	46	82–127	548.5			2.7×10^{-5}	7.2 (PBB-101)
Hexabromobiphenyls	36355-01-8	$C_{12}H_4Br_6$	42	128–169	627.4	72	11–3[b]	1.4×10^{-6}	8.0 (PBB-153)
Heptabromobiphenyls	35194-78-6	$C_{12}H_3Br_7$	24	170–193	706.3			1.1×10^{-7}	8.3 (PBB-180)
Octabromobiphenyls	27858-07-7	$C_{12}H_2Br_8$	12	194–205	785.2	200–255	20–30	8.7×10^{-9}	8.7 (PBB-194)
Nonabromobiphenyls	27753-52-2	$C_{12}H_1Br_9$	3	206–208	864.1			1.7×10^{-9}	9.1 (PBB-206)
Decabromobiphenyls	13654-09-6	$C_{12}Br_{10}$	1	209	943.0	380–386	Insoluble	3.2×10^{-10}	9.4 (PBB-209)

[a] Values are examples of one congener in the homologue group.

[b] Calculated using Advanced Chemistry Developement (ACD/Labs) Software VII.02 (©1994–2010 ACD/Labs).

[c] Tittlemier *et al.* (2002)

BZ, Ballschmiter & Zell; PBBs, polybrominated biphenyls

From IARC (1978), EFSA (2010)

Table 1.4 Trade names of commercial PBB mixtures

Main PBB congeners	Trade name
Hexabromobiphenyls	Firemaster FF-1
	Firemaster BP-6
	"Hexabromobiphenyl"
Octabromobiphenyls	BB-8
	Bromkal 80
	Bromkal 80–9D
	Octabromobiphenyl FR 250 13A
	Technical octabromobiphenyl
Decabromobiphenyls	Adine 0102
	Berkflam B-10
	Flammex B-10
	HFO 101
	Technical decabromobiphenyl

PBB, polybrominated biphenyl
From IPCS (1994)

1.2 Analysis

Given that the physical and chemical characteristics of PBBs are similar to those of PCBs, sampling techniques for PBBs are essentially identical to those described for PCBs. However, a considerably smaller body of scientific literature is available on PBBs than on PCBs, and not all environmental matrices have been studied.

As with all brominated flame retardants, samples should not be exposed to sunlight, since PBBs are unstable when exposed to ultraviolet radiation (Brinkman & de Kok, 1980).

1.2.1 Environmental and food samples

PBBs were analysed together with polychlorinated dibenzodioxins/polychlorinated dibenzofurans (PCDD/PCDFs), PCBs and polybrominated diphenyl ethers (PBDEs) in the same air samples (Wang *et al.*, 2010a). Particles and gaseous phase were collected on glass-fibre filters and polyurethane foam, respectively, as described for PCBs. After Soxhlet extraction with toluene, extracts were treated with acid and purified on acid silica. In a second clean-up step on alumina, several fractions were obtained, including fractions with non-polar PBBs/PCBs and polar PBBs/PCBs.

Most studies combine the analysis of PBBs with that of PBDEs, for example, for soil (Wang *et al.*, 2009) or sediment samples (de Boer *et al.*, 2003). After freeze-drying and sieving, the samples were mixed with copper for sulfur removal, as described for analysis of PCBs in soils and sediments, Soxhlet extracted, and cleaned up on silica-gel columns. Besides Soxhlet extraction, pressurized liquid extraction has also been used for sediment analysis (Zhao *et al.*, 2010). Clean-up processes included multilayer columns of acid, neutral and basic silica gel, as well as gel-permeation chromatography and subsequent treatment with sulfuric acid (de Boer *et al.*, 2003; Zhao *et al.*, 2010).

Water samples were analysed in terms of influent and effluent samples of waste-water treatment plants (de Boer *et al.*, 2003). The samples were filtered or centrifuged to separate suspended particulate matter from the water phase, and then treated as for sediment samples, i.e. Soxhlet extraction of the particulate phase, gel-permeation chromatography, acid treatment and clean-up with silica gel.

Several studies have analysed fish samples, with a focus on the most biaccumulative congener PBB-153. The samples were dried, either by freeze-drying (Gieroń *et al.*, 2010) or with sodium sulfate (de Boer *et al.*, 2003), and extracted using a Soxhlet apparatus (de Boer *et al.*, 2003; Zhu & Hites, 2004) or direct extraction with dichloromethane in an extraction column (Luross *et al.*, 2002). Lipids were removed by acid treatment, using acid silica gel (Gieroń *et al.*, 2010) or direct treatment with sulfuric acid (de Boer *et al.*, 2003). Further clean-up and fractionation techniques included gel-permeation chromatography, column clean-up with alumina or with neutral/basic silica and the dialysis through semi-permeable membrane devices (Gieroń *et al.*, 2010).

Table 1.5 Composition of commercial PBB mixtures

Composition	Commercial mixture (range of % bromination)			
	Hexabromobiphenyls	Octabromobiphenyls[a]		Decabromobiphenyls
Tetrabromobiphenyls	2–5			
Pentabromobiphenyls	1–11			
Hexabromobiphenyls	63–84	0	1–2	0–4
Heptabromobiphenyls	12–25	1–7	23–27	0–4
Octabromobiphenyls	0–2	25–57	46–72	0–7
Nonabromobiphenyls		0–28	34–65	2–11
Decabromobiphenyls		2–9	0–1	71–97

[a] The Working Group noted that the "octabromobiphenyls" include two classes of mixtures with different ranges of composition. In IPCS (1994), they are called "octanonabromobiphenyls."
PBB, polybrominated biphenyl
From de Kok *et al.* (1977), IPCS (1994)

Gieroń *et al.* (2010) also analysed other food products using this method; pure lipid samples (butter, pork adipose tissue) were melted before further processing. Analytical methods for PBBs in food were summarized by EFSA (2010), describing solvent extraction, lipid removal and additional clean-up by column chromatography.

1.2.2 Biological samples

Several studies have been conducted on the Michigan cohort, which was established in 1976 following the accidental contamination of cattle feed with PBBs and subsequent exposure of local residents (see Section 1.4). Human serum samples were analysed at enrolment in the cohort (1976–1978) and in the follow-up studies until 1993 (Givens *et al.*, 2007). After protein denaturation with methanol, PBBs were extracted with hexane:diethyl ether (1:1), and extracts were cleaned on Florisil (Burse *et al.*, 1980; Needham *et al.*, 1981). More recent blood analyses did not deviate much from these procedures, but applied a higher degree of automatization (Frederiksen *et al.*, 2010). The first step was generally protein denaturation, often using formic acid. Solid-phase extraction was a common extraction technique, followed by lipid removal using H_2SO_4 (Wang *et al.*, 2010b) or clean-up on acid and neutral silica (Sjödin *et al.*, 2004a) and/or Florisil (Sandanger *et al.*, 2007; Wang *et al.*, 2010b). Blood analyses have generally focused on PBB-153 as the congener with the most pronounced bioaccumulation.

For the analysis of human milk, EFSA (2010) described solvent extraction and solid-phase extraction, followed by the same clean-up method as for food samples. Adipose tissue has also been analysed for PBBs, in combination with PBDEs and PCBs (Fernandez *et al.*, 2007; Miceli *et al.*, 1985). The samples were Soxhlet-extracted using toluene or hexane:acetone. Lipids were removed on acid silica gel. Further clean-up included neutral and basic silica gel and a fractionation into different compound groups. Target PBBs and PBDEs were separated from PCDD/PCDFs on an activated carbon column and further cleaned up on alumina (Fernandez *et al.*, 2007), while separation of PCBs from the brominated compounds was achieved by different solvents eluting the compounds from the silica-gel column (Zhao *et al.*, 2009).

1.2.3 Instrumental analysis

As described for PCBs, the instrumental analysis of PBBs is basically independent of the original matrix, although selectivity and

sensitivity should be considered. It also is worth noting that PBBs often are analysed in conjunction with other substances, making multicompound methods desirable. For example, studies including the determination of dioxins and furans or other coplanar molecules besides PBBs have used high-resolution gas chromatography (HRGC) in combination with high-resolution mass spectrometry (HRMS) (Wang *et al.*, 2010a), which is a highly selective and very sensitive technique. Owing to these advantages, HRGC–HRMS has also been applied in analyses of environmental and biological samples that have combined determination of PBDEs and PBBs (Luross *et al.*, 2002).

Gas chromatography–mass spectrometry (GC–MS) with electron-capture negative ionization (ECNI) is a common method in the analysis of PBBs, providing high sensitivity (de Boer, 1999). However, PBB-153, the predominant congener in biological matrices, co-elutes with the PBDE BDE-154 on several GC columns. As both congeners are detected by the mass fragments m/z = 79 and m/z = 81, chromatographic separation must be achieved to avoid miscalculations, for example on a 60 m capillary column (Zhu & Hites, 2004). On the other hand, a shorter column is advisable for the determination of PBB-209, which is not stable at elevated temperatures (de Boer, 1999; Zhao *et al.*, 2009). As the GC–MS (ECNI) method relies on the detection of the bromide ion, the use of ^{13}C-labelled standards is excluded.

GC–MS with electron impact (EI) ionization has also been used for environmental and biological samples (Zhao *et al.*, 2009; Gieroń *et al.*, 2010), allowing detection of molecular ions and specific fragments. However, this technique is described as being 10 times less sensitive than GC–MS (ECNI) and GC with electron capture detection (ECD) (de Boer, 1999). GC–ECD was generally used in the early studies (Burse *et al.*, 1980), and although still applied in environmental and biological analyses (Wang *et al.*, 2009; Wang *et al.*, 2010b), is increasingly replaced by GC–MS techniques.

1.2.4 PXBs

Only few studies have analysed mixed chlorinated/brominated biphenyls, as recently reviewed by Falandysz *et al.* (2012). Eight native congeners and their ^{13}C-labelled analogues were commercially available for this analysis. Other studies, which rely on custom-made analytical standards, analysed fewer congeners (Ohta *et al.*, 2008a).

PXBs were generally analysed together with other compounds, primarily PCDD/PCDFs, by extending existing methods. Additional fractionation steps on carbon columns were included to isolate the PXB congeners. They were analysed by HRGC–HRMS using isotope dilution quantification, although not all studies used matching native and labelled congeners (Falandysz *et al.*, 2012).

PXBs have been analysed in food (Fernandes *et al.*, 2011), fish (Ohta *et al.*, 2008a) and human milk (Gómara *et al.*, 2011), focusing on five to eight congeners. Fernandes *et al.* (2011) described an extensive sample clean-up involving acid and basic silica gel and several carbon columns, to isolate non-*ortho* and mono-*ortho* PXBs, respectively.

1.3 Production and uses

Production of PBBs generally involves the reaction of biphenyl with bromine and chlorine in a solvent with aluminum chloride as a catalyst (Neufeld *et al.*, 1977). PBBs are also formed as impurities during the production of other brominated compounds. For example, PBBs are formed during the production of decabromodiphenyl oxide because of the presence of diphenyl as an impurity in the starting material, diphenyl oxide (Neufeld *et al.*, 1977). PBBs are also present as impurities in PBDEs (Hanari *et al.*, 2006).

Commercial PBB mixtures were manufactured primarily as flame retardants. In the USA and Europe, PBB mixtures were produced and sold commercially as products with a specific bromine content. Although these commercial products are generally referred to as "hexabromobiphenyl," "octabromobiphenyl," and "decabromobiphenyl," these are misnomers, since each commercial product contained numerous congeners with different numbers of bromine substitutions (see Section 1.1.2). The composition of commercial products varied substantially across lots and producers (Table 1.5), particularly for octabromobiphenyls, many of which may actually have consisted primarily of nonabromobiphenyls.

PBBs were produced by three companies in the USA during the 1970s only. One company in Michigan produced hexabromobiphenyl, and two companies in New Jersey produced octabromobiphenyl and decabromobiphenyl. Total production in the USA was estimated at 13 million pounds [5896 tonnes], 88% of which was hexabromobiphenyl (Table 1.6). Production of hexabromobiphenyl in Michigan was halted in 1974 subsequent to the contamination of animal feed (see Section 1.4), and production of octabromobiphenyl and decabromobiphenyl was discontinued a few years later (Neufeld *et al.*, 1977). In the United Kingdom, PBBs were produced until 1977; in Germany, until the mid 1980s; and in France, until 2000, with only decabromobiphenyl being produced in the later years (EFSA, 2010). No information was available on production volumes in Europe or elsewhere.

In addition to these commercial producers, a few speciality chemical companies produced PBBs with lower bromine content, mostly monobromobiphenyls and dibromobiphenyls, in small batches of 0.1–1 kg, to be used in functional fluids (Neufeld *et al.*, 1977).

The major uses of PBBs were in acrylonitrile-butadiene-styrene (ABS) plastics (used, for example, for housing television sets and other electronic machines), in coatings and lacquers, and in polyurethane foam. Based on a PBB content of 10%, an estimated 118 million pounds [53.5 tonnes] of PBB-containing ABS plastic could have been made during 1971–1975, which would be about 5% of the total production of ABS plastics during those years (Neufeld *et al.*, 1977). In these uses, PBB flakes were physically blended into the product, not chemically incorporated into a polymer (Neufeld *et al.*, 1977). This raises the concern that they could volatilize or leach out of the product (ATSDR, 2004).

Recently, PBBs were detected in electronic waste in cable coatings, stuffing powder for electronic components, and circuit boards, suggesting uses in such equipment. PBBs in these items consisted mostly of mono-, di-, or tribromobiphenyls (Zhao *et al.*, 2008). [The Working Group noted that this is not consistent with hexa-, octa-, and decabromobiphenyl being the only commercial mixtures with large-scale production and use. This suggests that PBBs of predominantly low bromine content may have been used in electronic equipment in China, which was previously unknown. The Working Group noted the small sample size.]

PXBs can be formed when chlorine and bromine are present during the combustion of PCBs or PBBs. PXBs are also contaminants of commercial PCB mixtures, resulting from the presence of bromine gas as a trace contaminant of the chlorine gas used in the production of PCBs. Dioxin-like PXBs can be formed during pyrolysis or photolysis of PBDEs. PXBs are not known to be produced intentionally (Falandysz *et al.*, 2012).

1.4 Environmental occurrence and human exposure

PBBs can enter the general environment from several sources: loss during production of PBBs, loss during manufacture of products containing PBBs, disposal and reprocessing

Table 1.6 Production volumes of commercial PBB mixtures in the USA

Year	Hexabromobiphenyls	Octa- and decabromobiphenyls	Total (tonnes)
1970	0.95	14.0	24
1971	84	14.0	98
1972	1007	14.5	1022
1973	1764	162	1927
1974	2214	48.0	2263
1975	0	77	77
1976	0	365	365
1977	0	> 0	> 0
Total (%)	5079 (88%)	> 7046 (12%)	> 5775 (100%)

PBB, polybrominated biphenyl
Adapted from DiCarlo *et al.* (1978)

of products containing PBBs, and accidental releases. Products from the 1970s that contained PBBs have generally reached the end of their useful life and would have been recycled, disposed of in landfills, or incinerated.

It was estimated that the production of 805 000 pounds [365 tonnes] of decabromobiphenyl in the USA in 1976 resulted in 5% loss to the environment: 900 pounds [408 kg] to air, 0.0037 pounds [1.7 g] to wastewater, and 40 250 pounds [18.3 tonnes] to landfills as solid waste (Neufeld *et al.*, 1977). [The wastewater calculation for decabromobiphenyl considered only the solubility of PBBs in water, which is low, and not the likelihood that solid PBB particles could also be discharged in wastewater.] Similar figures were not located on losses from production of hexabromobiphenyl, but discharges in 1974 from the plant in Saint Louis, Michigan, USA, were estimated at 0.11 kg per day (Archer *et al.*, 1979). [The hexabromobiphenyl mixture has a higher vapour pressure and a higher fraction of congeners with low bromine content, which generally would be more volatile.]

Contamination with PBBs has been high in Michigan, owing to accidental widespread contamination of farms, foods, and residents. In early 1973, several bags of the hexabromobiphenyl mixture "Firemaster" were mistaken for "NutriMaster," an animal feed supplement containing magnesium oxide. Both products were manufactured at the same plant. A shortage of preprinted paper bags at the plant led to 10–20 50-pound [22.7 kg] bags of Firemaster being packed in NutriMaster paper bags and sent to animal-feeding operations (Michigan Department of Community Health, 2011).

PBB concentrations in the contaminated feed were estimated to be between 4000 and 13 500 ppm [mg/kg]. In addition, there were four routes of indirect contamination with PBBs (Kay, 1977):

- Processing or mixing of clean feed in contaminated grain elevators (chicken feed became contaminated in this way).
- Incorporation of material from contaminated animals that died (and were sent to a rendering plant) into animal feed.
- Processing of contaminated milk into milk powder for feeding young animals.
- Swapping of feed by farms and feed mills.

The error was not discovered until April 1974, by which time the PBBs had entered the food chain through contaminated milk, eggs and other dairy products, contaminated beef products, and contaminated swine, sheep, and chickens. More than 500 Michigan farms were quarantined and 30 000 cattle, 1500 sheep, and 1.5 million chickens were destroyed. Inventories of 800 tons [725 tonnes] of animal feed, 18 000

pounds [8.1 tonnes] of cheese, 2500 pounds [1.1 tonnes] of butter, 5 million eggs, and 34 000 pounds [15.4 tonnes] of dried milk products were also destroyed (Michigan Department of Community Health, 2011).

PBBs have generally been replaced by PBDEs. PBBs, however, are present as impurities in PBDEs. On the basis of PBDE production and use in 2001, it was estimated that potential global annual emissions of PBBs would be 40 kg (Hanari *et al.*, 2006). [The Working Group noted that the Michigan incident involved 500–1000 pounds [225–450 kg] of PBBs.] There were few reports of recent concentrations of PBBs in environmental media; most investigations of brominated compounds have focused on PBDEs and newer brominated alternatives for use as flame retardants.

1.4.1 Environmental fate

In the environment, PBBs occur as mixtures of congeners whose compositions differ from that of the commercial products. This is because after release into the environment, composition changes over time because of partitioning, chemical transformation, and bioaccumulation. PBB congeners are highly persistent in the environment and in biological tissues. Air and water are the transport media.

Primarily hydrophobic, PBBs adsorb strongly to soils and sediments. Hydrophobic adsorption generally increases with the bromine content of the PBB congener and the organic content of the soil or sediment. In water, PBBs with high bromine content are less soluble and more likely to attach strongly to sediment. PBB congeners with low bromine content are more likely to be soluble in water. In air, PBB congeners are generally not very volatile, and are less volatile than the corresponding PCB congeners (Pijnenburg *et al.*, 1995).

PBBs are lipophilic and can be dissolved in solvents. Liquid solvents that may be present in landfills or contaminated sites are capable of solubilizing PBBs and carrying them to distant locations (ATSDR, 2011). PBBs are 200 times more soluble in landfill leachate than in distilled water, and more soluble in creek water than in purified water. These results are correlated with the levels of dissolved organic compounds (Lewis, 1981).

PBBs degrade slowly in the environment. In 1988, sediments from Pine River, Michigan, contained 10–12% PBB congeners that are not found in Firemaster, consistent with bromines being selectively removed from *meta* and *para* positions. Microorganisms are capable of debrominating PBB congeners, although this process can be inhibited by organic co-contaminants, petroleum products, and heavy metals. Ultraviolet light can degrade PBB congeners, especially at *ortho* positions (Pijnenburg *et al.*, 1995).

Bioconcentration and bioaccumulation are important processes for PBBs in water. Bioconcentration from water is more pronounced for PBBs with low bromine content. The pattern for bioaccumulation from food is more complex (Pijnenburg *et al.*, 1995).

1.4.2 Natural occurrence

PBBs and PXBs are not known to occur in nature.

1.4.3 Air and dust

In the past, PBBs were released into the air during manufacture. Air emissions through vents were reported to be $2–3 \times 10^{-6}$ mg/L (Neufeld *et al.*, 1977; Vorkamp *et al.*, 2005; Wang *et al.*, 2010a). PBBs were detected at a concentration of 6×10^{-11} mg/L in air samples near a PBB-manufacturing plant, although the same concentration was measured downwind and crosswind from the plant (DiCarlo *et al.*, 1978).

Another potential source of PBBs in air is from incineration of products containing PBBs. Pyrolysis of commercial hexabromobiphenyl

produces small amounts of lesser brominated biphenyls (Thoma & Hutzinger, 1987).

Near a municipal solid waste incinerator in Taiwan, China, PBB concentrations in air were reported as 149–556 fg.N/m^3 (Wang *et al.*, 2010a).

PBB-153 was not detected in house dust in Bavaria, Germany, with a limit of detection of 10 ng/g (Kopp *et al.*, 2012).

No other information was available on recent concentrations of PBBs in outdoor or indoor air.

PXBs have been found in exhaust gas from waste incinerators and in marine sediments in Japan (Ohta *et al.*, 2009).

1.4.4 Water, sediment, and sewage sludge

No data were available on recent concentrations of PBBs in surface water, groundwater, or sediment.

In the past, PBBs were released into water during manufacture. PBBs have been found in a variety of surface waters, groundwater, and sediments. This is most probably due to solid PBB particles being carried along with the water, as PBBs are rather insoluble in water. As might be expected, concentrations in river water and sediments tend to decrease with distance downstream from the source (Table 1.7). Although most sampling has occurred in and around PBB-production plants, PBBs have also been detected in wastewater from the production of decabromodiphenyl oxide (in which PBBs are a byproduct) and in effluents and sludge from a municipal wastewater-treatment plant (Neufeld *et al.*, 1977; Daso *et al.*, 2012).

Wastewater discharges from the Michigan Chemical Corporation plant provide an instructive example. In 1972, PBB particles were measured in wastewater from the plant at concentrations up to 98–503 µg/L. In 1974, after actions to reduce the discharge of PBB particles, concentrations of up to 100 µg/L persisted. In 1975, after PBB production was halted, concentrations as high as 150 µg/L were measured irregularly. In 1977, after removal of contaminated soil from bagging and loading areas of the plant, concentrations fell to below 1 µg/L (Hesse & Powers, 1978).

In 1999, PBBs were not found in suspended particulate matter, sediments, sewage treatment plant influents and effluents, fish, and mussels in the Netherlands (limit of detection, 0.1–1 µg/kg dry weight; 1–10 µg/kg for PBB-209) (de Boer *et al.*, 2003).

1.4.5 Soil

PBBs are found at nine sites on the United States Environmental Protection Agency's National Priorities List ("Superfund" sites), four of them in Michigan (ATSDR, 2011), including the site of the Michigan Chemical Corporation plant. In 1975, soil from bagging and loading areas of the Michigan Chemical Corporation plant contained PBBs at 3500 and 2500 mg/kg, respectively (Hesse & Powers, 1978) and soil near the two PBB-production plants in New Jersey, USA, contained PBBs at 40–3100 and 750–2800 µg/kg, respectively (DiCarlo *et al.*, 1978). Soil samples from 28 fields that received manure from Michigan's most highly contaminated dairy herds had the following distribution of PBB concentrations: below detection limit of 0.1 µg/kg, two fields; 0.1–0.9 µg/kg, six fields; 1–9 µg/kg, nine fields; 10–99 µg/kg, five fields; 100–371 (maximum) µg/kg, six fields. PBBs were not detected in two control farm fields. PBBs also were below the detection limit of 0.3 µg/kg in corn, alfalfa, and sudangrass that was being grown in the contaminated fields (Jacobs *et al.*, 1978).

Soil samples near facilities that processed PBBs in California and West Virginia, USA, contained PBBs at up to 36 000 and 12 µg/kg, respectively (Zweidinger & Pellizzari, 1980).

In 2007, PBB concentrations were measured in soil collected from four villages in China where electronic-waste disassembly sites were located. The median PBB concentration was

Table 1.7 Concentrations of PBBs in various environmental media

Medium	Site	PBB concentration	Reference
Wastewater	Original discharge from Michigan PBB plant	98–503 µg/L	Hesse & Powers (1978)
	After some action to reduce discharges	≤ 100 µg/L	Hesse & Powers (1978)
	After PBB production stopped	Erratic, ≤ 150 µg/L	Hesse & Powers (1978)
	After soil cleanup at plant	< 1 µg/L	Hesse & Powers (1978)
Wastewater	Decabromodiphenyl oxide production	< 0.1–10 µg/L	Neufeld *et al.* (1977)
Storm sewer water	Near New Jersey PBB plant	92 µg/L	DiCarlo et al. (1978)
Swamp water	Runoff from New Jersey PBB plant	135 µg/L	DiCarlo et al. (1978)
River water	Near effluent discharge of Michigan PBB plant	13 µg/L	Archer *et al.* (1979)
	13 km downstream	0.01 µg/L	Archer et al. (1979)
	12 miles downstream of Michigan PBB plant	0.01–0.07 µg/L	Hesse & Powers (1978)
	25–29 miles downstream	ND (< 0.1 µg/L)	Hesse & Powers (1978)
Sediment	Near New Jersey PBB plant	100 mg/kg	Archer *et al.* (1979)
	At Michigan PBB plant	77 mg/kg	Hesse & Powers (1978)
	Just downstream of plant	6.2 mg/kg	Hesse & Powers (1978)
	29 miles downstream	0.1 mg/kg	Hesse & Powers (1978)
Groundwater	Near landfill from Michigan PBB plant	0.1–0.2 µg/L	DiCarlo *et al.* (1978)
Drainage ditch, catch basin	Near landfill from Michigan PBB plant	1.2 mg/kg	DiCarlo et al. (1978)
Effluent	Wastewater treatment plant in South Africa	< 18.4 ng/L	Daso *et al.* (2012)
Sewage sludge	Wastewater treatment plant in South Africa	< 9.97 ng/g	Daso et al. (2012)

ND, not detected; PBBs, polybrominated biphenyls

22 µg/kg (range, 18–58 µg/kg; n = 6) compared with 11 µg/kg (range, 8–19 µg/kg; n = 3) in a remote village at a distance of 30 km where there were no electronic-waste operations. Mono-, di-, and tribromobiphenyls predominated, with PBB-2 being the single most abundant congener (Zhao *et al.*, 2008).

Soils from urban and rural sites in the United Kingdom contained dioxin-like PXBs, with concentrations an order of magnitude greater in urban soil than in rural soil. Concentrations of four mono-*ortho* PXBs were 0.90, 0.49, and 0.17 ng/kg in urban soil, and 0.050, 0.025, and 0.024 ng/kg in rural soil (Fernandes *et al.*, 2011).

1.4.6 Bioaccumulation in wildlife and plants

Field studies in several species show that PBBs are taken up by wildlife. Near the Michigan Chemical Corporation plant, PBBs have contaminated fish in the Pine River downstream from the plant. PBBs were detected in 25 out of 27 composite samples, where each sample represented one out of seven fish species taken at one out of four sampling stations. The highest concentration was 1.33 mg/kg in skinless carp fillets. PBBs were not detected in fish samples collected upstream of the plant above a dam that prevents upstream fish movement, and PBBs were not detected in fish samples from a nearby river. PBBs were detected in the majority of wild ducks collected within 2 miles of the plant. Near a PBB-production plant in New Jersey, a turtle was found to contain hexabromobiphenyl at 20 µg/kg. More recently, PBB congeners, predominantly PBB-153, were detected in lake trout from the Great Lakes (DiCarlo *et al.*, 1978; Hesse & Powers, 1978; Luross *et al.*, 2002).

The strong bioaccumulation potential of PBBs was demonstrated in caged fish in the Pine River near the Michigan Chemical Corporation plant. After 2 weeks of exposure, concentrations in caged fathead minnows were up to 10 000 times those in the surrounding river water. No

PBBs were detected in fish sampled at a control station 3 miles upstream of the plant (Hesse & Powers, 1978).

PBBs have been measured in a variety of marine species. These positive measurements, made at sites far from industrial sources of PBBs, indicate that PBBs can be transported great distances. The detection of PBBs in sperm whales indicate that these compounds have reached deep ocean waters, as sperm whales are not usually found in shallow seas (Jansson *et al.*, 1987, 1993; de Boer *et al.*, 1998). [It is noteworthy that whenever a species has been sampled in the same area in different years, the levels have increased.]

PBB-153 was detected in the eggs of six species of wild aquatic birds, one species of wild terrestrial bird, and two species of captive birds in China. Levels ranged from non-detectable to 0.7 ng/g lipid weight (Vorkamp *et al.*, 2005; Gao *et al.*, 2009).

PBBs were taken up by root vegetables grown in soil artificially contaminated with PBBs. Most of the residue was on the vegetable surface and could be removed by dipping in acetone. Uptake was higher by plants grown in a sandy soil than in a clay soil with higher organic content. This is consistent with the tendency of PBBs to adsorb to soils with high organic content. No PBBs were detected in orchard grass or in carrot tops (Jacobs *et al.*, 1976; Chou *et al.*, 1978; DiCarlo *et al.*, 1978).

1.4.7 Food and estimated dietary intake

Soon after the Michigan incident was discovered, sampling on contaminated farms revealed BBP concentrations as high as 595 mg/L in milk, 4600 mg/kg in poultry tissue, 60 mg/kg in eggs, and 2700 mg/kg in cattle tissue (Kay, 1977).

In milk from contaminated dairy herds, the concentration of PBBs was estimated to have reached 6000 mg/L after 15 days exposure, declining to 1800 mg/L 15 days after exposure ceased, and to 160 mg/L after another 230 days (Fries *et al.*, 1978).

Based on monitoring of PBBs in food and a call for data, the European Food Safety Authority (EFSA) evaluated results on 794 food samples collected during 2003–2009 from Belgium, Estonia, France, Ireland, Spain, and the United Kingdom (5643 analytical results covering 16 PBB congeners). Due to the large number of non-detects for individual congeners in individual samples, EFSA focused the analysis on seven congeners: those with less than 80% non-detects, plus the three coplanar PBBs PBB-77, PBB-126, and PBB-169. The EFSA analysis provided the ranges of these PBB congeners in four food categories (Table 1.8; EFSA, 2010).

Based on recent estimates of mean and high dietary exposure to the different food categories, EFSA calculated average and high-end intakes of five PBB congeners from food. For children aged 1–3 years, the principal source was milk, with an intake of 32 or 64 pg/kg bw per day for average or high-end consumers, respectively. For children aged 3–6 years, the principal source was fish and seafood, with an intake of 15 or 66 pg/kg bw per day for average or high-end consumers, respectively. For adults, the principal source was fish and seafood, with an intake of 8 or 40 pg/kg bw per day, respectively. Food supplements would add another 39 pg/kg bw per day (Table 1.9; EFSA, 2010). [Including only five congeners in the analysis could lead to a substantial underestimate of intake, especially if a potent congener were omitted because it is not widely distributed across a broad food category.]

PXBs were detected in nine species of domestic or imported fish and one species of marine mammal from food markets in Japan. Toxic equivalency (TEQ), calculated as a weighted sum of the concentrations of five non-*ortho* congeners, ranged from 0.09 to 1.3 pg/g wet weight. When compared with TEQs calculated as a weighted sum of the concentrations of 12 PCB congeners, the predicted toxicity levels attributable to PXBs or PCBs were generally within one order of magnitude. The authors concluded that

Table 1.8 Mean concentration (pg/g wet weight) of seven PBB congeners in foods in Europe

PBB congener	Meat, meat products		Milk, dairy products		Fish, seafood		Food for infants, small children	
	LB	UB	LB	UB	LB	UB	LB	UB
PBB-49	–	–	–	–	1.32	1.52	–	–
PBB-52	0.06	0.39	0.01	0.58	4.19	4.31	–	–
PBB-101	0.06	0.39	0.01	0.58	1.55	1.86	–	–
PBB-153	–	–	–	–	0.81	18.9	0	7.64
PBB-77[a]	0.0002	0.0055	0	0.0051	0.0168	0.0226	–	–
PBB-126[a]	0.0045	0.0107	0	0.004	0.0005	0.0087	–	–
PBB-169[a]	0	0.0077	0	0.0071	0	0.0088	–	–

[a] Original data on non-*ortho* PBBs were reported with considerably lower LOQs. Therefore the number of digits after the decimal point has been extended to four in this table, for descriptive reasons.
LB, lower bound; PBB, polybrominated biphenyl; UB, upper bound
From EFSA (2010)

dioxin-like PXBs cannot be considered a negligible contributor to human health risks. The authors also remarked that the lack of availability of analytical standards made it impossible to identify and quantify most PXB congeners (Ohta *et al.*, 2008b). PXBs have been detected in seal blubber in ng/g lipid concentrations (Falandysz *et al.*, 2012).

Non-*ortho* and mono-*ortho* PXBs have been detected in several foods in the United Kingdom, including soft cheese, cow milk, duck eggs, lamb, liver, vegetables, river fish, and marine fish (Fernandes *et al.*, 2011).

1.4.8 Exposure of the general population

In 1976–1977, venous blood samples were drawn from several groups of Michigan residents and analysed for PBBs with a limit of detection of 1 µg/L. They showed a wide range of concentrations within each group of residents, and distinctly higher mean concentrations for three groups: chemical workers engaged in PBB production and their families, residents of quarantined farms, and direct recipients of products from such farms (Table 1.10; Landrigan *et al.*, 1979). [The Working Group noted that the inclusion of family members of chemical workers was likely to have reduced the reported levels for the chemical workers: while Table 1.10 (Landrigan *et al.*, 1979) shows a range of non-detect to 1240 µg/L for 216 chemical workers and their family members, Table 1.11 (Anderson *et al.*, 1978a) shows that none of the 55 chemical workers had a level less than 1.1 µg/L.]

In another report, the distribution of serum PBB concentrations in Michigan chemical workers was shown to be distinctly higher than that of farm residents (Table 1.11; Anderson *et al.*, 1978a).

In the same study, maternal serum, cord serum, and milk were sampled for 65 Michigan mothers potentially exposed to PBBs. They showed a wide range of PBB concentrations and a strong bioaccumulation of PBBs in human milk (Table 1.12; Landrigan *et al.*, 1979).

In 1993, PBBs and other persistent compounds were measured in the serum of people who reported eating at least one meal per week of sport fish caught in the Great Lakes. The overall mean serum PBB concentration in 30 subjects was 0.4 µg/L. When stratified by lake, serum concentrations were highest for people who ate fish from Lake Huron (mean, 0.6 µg/L; range, 0.1–1.7 µg/L), followed by Lake Michigan (mean, 0.4 µg/L; range, 0.04–1.0 µg/L) and Lake Erie (mean,

Table 1.9 Estimates of daily exposure to PBBs from food in Europe

Population	Food category	PBB congener	Average consumers (pg/kg bw per day)		High consumers (pg/kg bw per day)	
			LB	UB	LB	UB
Infants	Human milk	PBB-153	[620, 920]	[920, 1400][a]	–	–
	Ready-to-eat meal	PBB-153	–	0.17, 0.64[b]	–	–
Children aged 1–3 yr	Milk and dairy products	PBB-52	0.34	16.1	0.69	32.1
		PBB-101	0.41	16.2	0.82	32.3
Children aged 3–6 yr	Fish and other seafood	PBB-49	0.76	0.88	3.28	3.79
		PBB-52	2.44	2.50	10.4	10.7
		PBB-77	0.01	0.01	0.04	0.06
		PBB-101	0.90	1.08	3.86	4.63
		PBB-153	0.47	11	2.01	47
	Meat and meat products	PBB-52	0.23	1.66	0.42	2.97
		PBB-101	0.23	1.66	0.42	2.97
Adults	Fish and other seafood	PBB-49	0.39	0.45	1.97	2.28
		PBB-52	1.23	1.26	6.27	6.45
		PBB-77	0.01	0.01	0.03	0.03
		PBB-101	0.46	0.54	2.32	2.78
		PBB-153	0.24	5.53	1.21	28.2
	Meat and meat products	PBB-52	0.1	0.74	0.25	1.76
		PBB-101	0.1	0.74	0.25	1.76
	Milk and dairy products	PBB-52	0.05	1.91	0.1	4.84
		PBB-101	0.04	1.91	0.12	4.86
Adults; specific groups of the population	Fish with > 8% fat; daily intake of 179 g fishmeat	PBB-49	–	–	9.61	11.22
		PBB-52	–	–	34.4	35
		PBB-77	–	–	0.06	0.09
		PBB-101	–	–	12.2	14.1
		PBB-153	–	–	4.33	89
	Supplements with fatty acids daily intake of 15 mL	PBB-49	–	–	2	10.4
		PBB-52	–	–	3	4.5
		PBB-77	–	–	0.01	0.02
		PBB-101		–	3	4.8
		PBB-153	–	–	3.8	18.9

[a] Results reported from a study in Finish and Danish human milk samples, respectively (Shen *et al.*, 2008); the values refer to the mean intake for average and high consumers.

[b] Those estimates refer to two upper bound exposures estimated from the only two available consumption surveys.

bw, body weight; LB, lower bound; PBBs, polybrominated biphenyls; UB, upper bound; yr, year

From EFSA (2010)

0.2 µg/L; range, 0.06–0.7 µg/L). When stratified by state, serum concentrations were highest for residents of Michigan (mean, 0.7 µg/L; range, 0.11–1.7 µg/L), followed by Ohio (mean, 0.2 µg/L; range, 0.06–0.7 µg/L) and Wisconsin (mean, 0.05 µg/L; range, 0.04–0.06 µg/L). The stronger contrasts by state are consistent with Michigan dairy products being the source of PBB contamination and with Wisconsin producing most of its own dairy products (Anderson *et al.*, 1998). [Michigan's Lower Peninsula has long shorelines on Lake Michigan and Lake Huron, and a very short shoreline on Lake Erie. Water from Lake Michigan drains into Lake Huron, which drains

Table 1.10 Serum concentrations of PBBs in residents exposed as a result of the Michigan incident

Population group	Participation rate (%)	*n*	Serum concentration (μg/L)		
			Range	Mean	Median
PBB chemical workers and their families	78.0	216	0–1240	43.0	4.5
Residents on quarantined farms	95.6	1750	0–1900	26.9	4.0
Direct recipients of food products from quarantined farms	95.1	1114	0–659	17.1	3.0
Residents on farms with PBB contamination below quarantine limits	95.0	44	1–13	3.5	2.0
Self-referred residents on farms with PBB contamination below quarantine limits or persons who had eaten food produced on such farms	–	242	0–24	3.5	2.0
Self-referred volunteers who had no direct connection with contaminated farms	–	273	0–111	3.2	1.0
Total		3639	0–1900	21.2	3.0

n, total number; PBBs, polybrominated biphenyls
From Landrigan *et al.* (1979). Copyright (c) 1979, John Wiley and Sons.

into Lake Erie. The Pine River, which borders the Michigan Chemical Corporation plant, flows into Lake Huron (Fig. 1.3).]

Serum PBB concentrations were measured in two cohorts of Michigan children: a "farm exposure" cohort consisting of 87 children enrolled in long-term studies of PBB- or PCB-contaminated farm products and a "fish exposure" cohort consisting of 236 children born to women who had consumed PBB-contaminated fish from Lake Michigan. Serum PBB concentrations were measured in the early 1980s when the children were aged 4 years. The percentages of children in the farm and fish exposure cohorts who had detectable serum PBBs (> 1 μg/L) were 21% and 13%, respectively. Significant predictors of serum PBB concentrations in children aged 4 years were weeks of nursing, PBB concentrations in maternal milk, and PBB concentrations in cord serum (Table 1.13; Jacobson *et al.*, 1989).

In the Michigan Long-Term PBB Study, 27% of children born to mothers exposed to PBBs through contaminated food had detectable serum PBB concentrations (> 1 μg/L). Risk factors for detectable serum PBB concentrations were maternal serum concentrations of 8 μg/L or more, nursing for 5.5 months or more, maternal age at childbirth of 28 years or more, and being born during the period of PBB exposure. Infants who nursed for 5.5 months or more were six times more likely to have detectable concentrations of

Table 1.11 Distribution of serum concentrations of PBBs in people exposed as a result of the Michigan incident

Group	*n*	Percentage with each group of serum concentrations (%)				
		0–1.1 μg/L	1.1–9.9 μg/L	10–99.9 μg/L	100–999 μg/L	> 1000 μg/L
PBB chemical workers	55	0	51	31	13	5
Farm residents	524	23	59	14	4	0.4
Random male farmers and consumers	109	12	64	17	6	1

PBBs, polybrominated biphenyls
Adapted from Anderson *et al.* (1978a)

Table 1.12 Concentrations of PBBs in maternal serum, cord serum, and breast milk in residents exposed as a result of the Michigan incident

Group	*n*	PBB concentration (μg/L)			Ratio to maternal serum (range)
		Range	Mean	Median	
Maternal serum	52	0–1150	26.2	2.5	–
Cord serum	58	0–104	3.2	1.0	7.04[a] (1.5–10.3)
Milk (lipid basis)	32	32–93 000	3614	225	122.0 (62.2–256.7)

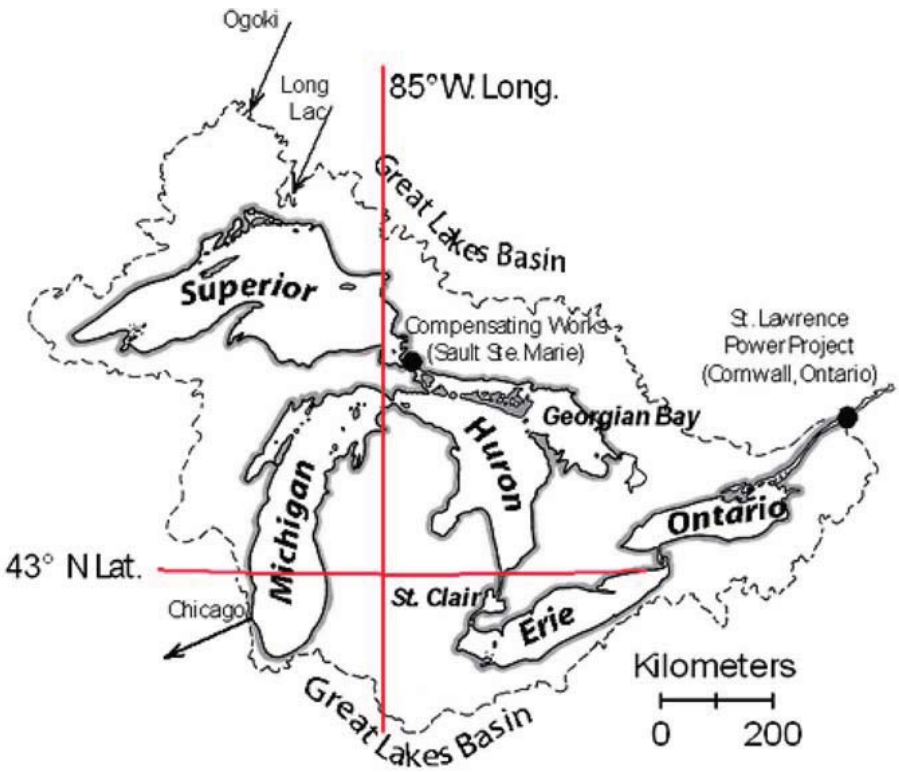
[a] [7.04 was reported by the authors, but this may refer to an inverse ratio]
PBBs, polybrominated biphenyls
Adapted from Landrigan *et al.* (1979). Copyright © 1979, John Wiley and Sons.

serum PBBs (95% CI, 2.0–19.6) (Joseph *et al.*, 2009).

Three out of nine samples of human hair [inferred to be from near the Michigan or the New Jersey PBB plant] contained PBBs at concentrations of 0.03, 1, and 2 ppm (Archer *et al.*, 1979).

Apart from the Michigan incident, several surveys have reported concentrations of the congener PBB-153 in the general population (Table 1.14). Analysis of data from *National Health and Nutrition Examination Survey* (NHANES) 2003–2004 indicated that PBB-153 was detected in 83% of samples (Sjödin *et al.*, 2008). Nonetheless, analysis of archived serum pools indicated that PBB-153 concentrations had been decreasing in the USA, the only country

Fig. 1.3 The Great Lakes basin area



From NOAA, Great Lakes Environmental Research Laboratory (GLERL, 2014)

Table 1.13 Serum concentrations of PBBs in children (age 4 years) born to Michigan mothers who ate contaminated farm products or fish

Cohort	*n*	Percentage of mothers with serum concentration > 1 ng/mL (%)	Serum concentration (ng/mL)	
			Mean	Range
Exposure from farm products	80	21.3	2.95	1.0–9.5
Exposure from fish	205	12.7	2.44	1.0–6.4

PBBs, polybrominated biphenyls
Adapted from Jacobson *et al.* (1989)

with multiple reports; in contrast, concentrations of the PBDEs that replaced PBBs have been increasing (Sjödin *et al.*, 2004b). One survey from Sweden reported much lower levels of PBBs than in the USA (Sjödin *et al.*, 2001). [A difficulty in interpreting PBB-153 concentrations is that this congener co-elutes with PBDE-154.]

In 2007, PBBs were detected in 90% and 50%, respectively, of maternal plasma and umbilical-cord plasma samples from women in Denmark with median PBB-153 concentrations of 181 and 68.6 pg/g lipid weight (Frederiksen *et al.*, 2010).

In 2003, PBB concentrations in human adipose tissue were collected from 20 women undergoing surgery for malignant and benign diseases in Spain. The mean sum of concentrations of seven PBB congeners was 0.358 ng/g lipid, with PBB-153 contributing 79% (Fernandez *et al.*, 2007). The ratio between human serum and adipose concentrations was estimated to be between 1:140 and 1:260 (Hakk & Letcher, 2003).

In 2007, PBB concentrations were measured in human hair collected from four villages in China where electronic-waste disassembly sites were located. Operations included recovering metals by burning cables, stripping metals in open-pit acid baths, and removing electronic components from circuit boards by heating over a grill, resulting in leakage, evaporation, runoff, and leaching of chemicals. PBB concentrations were elevated in two of these villages, compared with a control village 30 km away where there were no electronic-waste operations. Mono-, di-, and tribromobiphenyls predominated, with PBB-2 being by far the single most abundant congener (Table 1.15; Zhao *et al.*, 2008). In tissue samples of cancer patients in the same area, PBBs were detected in all samples of kidney, liver, and lung (n = 19, 55, and 7 samples, respectively). Median concentrations of PBBs in these tissues were 194, 193, and 145 ng/g lipid, respectively (Zhao *et al.*, 2009).

PXBs were detected in milk from seven mothers in Japan, 5 and 30 days after delivery. TEQs, calculated as a weighted sum of the concentrations of five non-*ortho* congeners, ranged from 0.42 to 1.41 pg/g (Ohta *et al.*, 2007). In a second study, five dioxin-like PXBs were measured in 20 mothers in Japan, 1 week after delivery. The sum of concentrations of five non-*ortho* congeners ranged from 12 to 350 pg/g lipid weight, with an average of 57 pg/g. The authors suggested that seafood was an important source of these congeners, as 3′,4′,5′-tribromo-3,4-dichlorobiphenyl was a major congener seen in fish and in human milk (Ohta *et al.*, 2008a).

PXBs were detected in milk from nine mothers in Madrid, Spain. The sum of concentrations of five non-*ortho* and three mono-*ortho* congeners was 0.45 pg/g lipid weight (Gómara *et al.*, 2011).

1.5 Occupational exposure

Historically, workers involved in the production of PBBs, PBB-containing plastics, and PBB-containing plastic products could have

Table 1.14 Concentrations of PBB-153 in human serum from surveys not directly related to the Michigan incident

Group, country	Year	*n*	Concentration (ng/g lipid)		Reference
			Median	Range	
Blood donors, USA	1988	12	19 pmol/g	4.2–84	Sjödin *et al.* (2001)
Female cleaners, Sweden	1997	20	0.59 pmol/g	0.25–1.4	Sjödin *et al.* (2001)
Archived serum pools, USA	1985–9	9	8.0	2.6–9.4	Sjödin *et al.* (2004b)
	1990–4	14	5.3	1.0–8.6	
	1995–9	10	4.7	1.9–10	
	2000–2	7	3.3	1.4–5.5	
NHANES, persons aged ≥ 12 years, USA	2003–4	2062	2.3	–	Sjödin *et al.* (2008)

n, total number; NHANES, National Health and Nutrition Examination Survey; PBB, polybrominated biphenyl

been exposed to PBBs via inhalation of dust and vapour, and/or via dermal contact.

After the Michigan incident in 1973, several studies showed that workers in PBB industries were exposed to high concentrations of PBBs. Several of these studies also showed high exposure among workers on dairy farm from the surrounding areas (Bekesi *et al.*, 1979a; Landrigan *et al.*, 1979; Stross *et al.*, 1979, 1981; Wolff *et al.*, 1979b). The Michigan population was more highly exposed than populations in other states.

In one PBB-manufacturing plant in the USA, 8 hour time-weighted average (TWA) air concentrations of PBB of 0.18 and 0.23 mg/m^3 were reported in 1977 (Bialik, 1982). These samples were collected in the manufacturing area and comprised mostly decabromobiphenyls. Surface-wipe measurements showed concentrations of up to 8 mg/100 cm^2. One surface-wipe sample collected on top of a table in the eating area had 0.1 mg/100 cm^2, which showed that in addition to inhalation and dermal routes of exposure, hand-to-mouth exposure was also possible. At the time of the survey, 95% of plant production consisted of decabromobiphenyl (18%) and decabromobiphenyl oxide (77%).

Several studies reported PBB concentrations in serum and adipose tissues (Table 1.16). Analysis of blood from employees at a hexabromobiphenyl-manufacturing company showed concentrations from 0.015 mg/L (after 3 months of exposure) to 0.085 mg/L (after 26 months of exposure) ($n = 6$), and of 0.006 mg/L in a supervisor employed for 38 months (Kay, 1977).

A study of exposure among PBB-manufacturing workers at another plant in the USA presented a detailed comparison of serum PBB concentrations by type of work activity (Bahn *et al.*, 1980a). A significantly higher number of PBB workers had detectable PBB concentrations compared with other workers (steelworkers and wiremen; 35.9% compared with 12.2%); also, the PBB workers had significantly higher serum PBB concentrations.

A clinical study including 55 exposed Michigan farm residents, 11 Michigan chemical workers and 46 non-exposed Wisconsin farmers showed that 7 out of 10 non-production workers (who did not participate in the production and handling of PBBs) had plasma concentrations of < 1 ng/mg (0.13–0.23 ng/mg protein) (Bekesi *et al.*, 1979a), while four production workers (who worked in the production and bagging section of the plant for several years, having been directly exposed to PBBs) had a PBB plasma concentration of around 10 ng/mg protein.

Clinical findings were reported for workers ($n = 55$) who manufactured Firemaster BP-6 from 1970 to 1974 in the USA (Anderson *et al.*, 1978a).

Table 1.15 PBB concentrations in human hair collected in villages around electronic waste-disassembly sites in China

Village	*n*	Concentrations (ng/g)	
		Median	Range
Tongshan	8	26	18–41
Panlang	11	29	14–55
Xiazheng	9	44	20–66
Xinqiu	8	58	24–103
Yandang (control)	4	26	22–32

PBBs, polybrominated biphenyls
Adapted from Zhao *et al.* (2008)

Other halogenated fire retardant chemicals were also produced at this plant. All 250 employees were invited to participate in the study, in particular those who had worked directly in the PBB-production area. Serum PBB concentrations were reported in ranges: 28 workers had serum PBB concentrations of 1.1–9.9 mg/L, 17 workers had 10–99.9 mg/L, 7 workers had 100–999.9 mg/L, and three workers were above 1000 mg/L.

In a study of liver function among farmers (n = 364) in Michigan after the accident, Anderson *et al.* (1978b) found the distribution of serum PBB concentrations to be: non-detectable–0.2 μg/L, 16 farmers; 0.21–1.0 μg/L, 69 farmers; 1.1–5.0 μg/L, 169 farmers; 5.1–10.0 μg/L, 52 farmers; and > 10.0 μg/L, 58 farmers.

One study assessed the distribution of PBB homologues (penta-, hexa-, and heptabromobiphenyls) in sera from dairy farmers and chemical-manufacturing workers. The relative concentration of two pentabromobiphenyls, both found in the Firemaster FF-1, differed widely between the two groups (Wolff & Aubrey, 1978). This would suggest different levels of exposure to the same mixture, but also that the mixture had been transformed between PBB manufacture and reaching the dairy farm, different routes of exposure, with farmers ingesting PBB partially metabolized in the animal food source. Compared with the original chemical product, one pentabromobiphenyl congener was not found in serum, possibly due to its relative ease of metabolism and excretion.

In the early 1990s, China started to process imported electronic waste ("e-waste") such as scrap metals, obsolete electric capacitors, household appliances, electric generators, and cable wires. Currently, 90% of all e-waste is imported from Japan, the USA, western European countries, and the Russian Federation. The recycling operations involve open-air burning, acid leaching, and physical dismantling by hammer, chisel, screwdriver, and bare hands. In 2008–2009, Chinese workers in the e-waste recycling industry were surveyed for serum levels of thyroid hormone, thyrotropin (thyroid-stimulating hormone), and brominated flame retardant (Wang *et al.*, 2010b). Workers exposed occupationally to brominated flame retardant during dismantling and recycling activities, non-occupationally exposed people, and controls were included in the study. The concentration of PBBs in sera of these occupationally exposed workers was 3.02 ng/mL plasma (n = 239). This value was lower than for farmers in the area surrounding the e-waste site [ΣPBB, 4.34 ng/mL plasma (n = 39)], but higher than for the controls [ΣPBB, 1.43 ng/mL plasma (n = 116)].

Table 1.16 Concentrations of PBBs in serum and adipose tissue of occupationally exposed workers

Year	Group	*n*	Concentration in µg/L				Reference
			Geometric mean	Median	Range	Limit of detection	
Serum – farm workers							
1976	Exposed farm workers	46	14	NR	1–180	NR	Stross *et al.* (1979)
Serum – chemical manufacturing[a]							
1975	Workers	7	NR	NR	6–85	NR	Kay (1977)
1976	Workers	28	48	NR	NR	NR	Stross *et al.* (1981)
1976	Workers, all	55	NR	NR	1.1–1729	NR	Wolff & Aubrey (1978), Wolff *et al.* (1979a)
	Production workers	10	603.9	108.4	NR	1	
	Non-production workers	45	16.5	6.1	NR	1	
1976	Workers	14	230	12	1–1530	< 0.2	Wolff *et al.* (1979b)
1978	Workers	14	227	22	1–1363	< 0.2	Wolff et al. (1979b)
1976–7	Workers and families	216	43.0	4.5	ND–1240	1	Landrigan *et al.* (1979)
1975–80	Workers (men)	29	25.4	20	1–1200	1	Eyster *et al.* (1983)
1978	Workers	35	NR	NR	ND–1340	NR	Bahn *et al.* (1980a, b)
1979	Production workers	4	NR	NR	10–10.2	1	Bekesi *et al.* (1979a)
1979	Non-production workers	7	NR	NR	0.13–0.23	1	Bekesi et al. (1979a)
Serum – e-waste recycling							
2008–9	Workers	236	*ΣPBB*				Wang *et al.* (2010b)
			3.02	NR	NR	NR	
			PBB-209				
			0.34	NR	ND–2.54	NR	
			PBB-103				
			0.67	NR	ND–4.96	NR	
			PBB-77				
			2.01	NR	ND–189.17	NR	
Adipose tissue – chemical manufacturing[a]					*(µg/kg)*		
1976	Production workers	7	196 490	46 940	5 000–580 000	500	Wolff *et al.* (1979a)
	Non-production workers	20	3880	2490	500–10 000	500	
1975–80	Workers (men)	29	5290	6000	400–350 000	1	Eyster *et al.* (1983)
NR	Workers	25	9330	NR	[300–80 000]	NR	Brown *et al.* (1981)
NR	Workers	28	NR	NR	12 820	NR	Stross *et al.* (1981)

[a] All plants studied were in Michigan and manufactured primarily "hexabromobiphenyl", except for the study by Bahn *et al.* (1980b), which studied a plant in New Jersey manufacturing mono- and deca-bromobiphenyl.
ND, not detected; NR, not reported; PBBs, polybrominated biphenyls

1.6 Regulations and guidelines

In 1974, the United States Food and Drug Administration established tolerance limits of 1.0 mg/kg (fat-weight basis) for PBBs in milk and meat fat, and 0.1 ppm in eggs, which were soon afterwards lowered to 0.3 mg/kg and 0.05 ppm, respectively (ATSDR, 2004).

In 1983, the European Union directed that PBBs may not be used in textile articles intended to come in contact with the skin (EFSA, 2010).

In 2002, the European Parliament directed that electrical and electronic equipment in the European Union may not contain PBBs at concentrations greater than 0.1%. Only six substances are restricted to such a degree, the other five being lead, mercury, cadmium, hexavalent chromium, and PBDEs. Plastic containing brominated flame retardants must be removed and treated separately from waste electrical and electronic equipment (EC, 2011).

The commercial product "hexabromobiphenyl" has been included in the Convention on Long-range Transboundary Air Pollution since 1998, and in the Stockholm Convention on Persistent Organic Pollutants since 2009. Parties to these conventions have agreed to take measures to eliminate the production and use of these pollutants (EFSA, 2010).

PBBs are not regulated as contaminants in food or as undesirable substances in animal feed. No other national or international regulations or guidelines were available.

2. Cancer in Humans

Data on the carcinogenicity of PBBs in humans are available from follow-up of a cohort of individuals in Michigan, USA, who were exposed as a result of an industrial incident in 1973 in which PBBs were accidentally mixed with cattle feed, and from one occupational study of chemical workers potentially exposed to several brominated compounds.

The Michigan cohort includes residents of contaminated farms, PBB-manufacturing workers, and people who consumed food from contaminated farms. The 3899 participants were followed by the Michigan Department of Public Health (Landrigan *et al.*, 1979). Two nested case–control studies were designed in this cohort. Hoque *et al.* (1998) evaluated the association between site-specific risks of cancer and serum PBB concentrations. In the follow-up of the cohort until 1993, 195 primary cancers were identified in 187 people. Controls were 696 randomly selected cancer-free individuals who were frequency matched to cases by sex and age. Baseline serum PBB concentrations were measured using standard methods. This study found a dose–response relationship for cancer of the digestive system (liver, stomach, oesophagus, pancreas). Odds ratios (ORs) for digestive cancers were 8.23 (95% CI, 1.27–53.3), 12.3 (95% CI, 0.80–191), and 22.9 (95% CI, 1.34–392), respectively, for serum PBB categories of 4–20 ppb, 21–50 ppb, and > 50 ppb after adjustment for age, sex, family cancer history, cigarette smoking, alcohol drinking, and baseline serum PCB concentration. Odds ratios for cancer of the breast based on the same categorization of exposure were 2.41 (95% CI, 0.92–6.30), not estimable due to zero exposed cases, and 1.39 (95% CI, 0.16–12.5). The analysis for serum PBB concentration and risk of lymphoma adjusted for all covariates except family history and baseline serum PCB concentration also showed a dose–response relationship, with corresponding odds ratios of 3.85 (95% CI, 0.32–46.2), 19.6 (95% CI, 1.52–253), and 48.9 (95% CI, 4.09–585). [This was a unique cohort that provided important information about the effects of PBBs. Positive associations were observed, but quantitative interpretation of the findings was hampered by small numbers, particularly in the analysis of lymphoma, where the referent group contained

only one case, leading to very wide confidence intervals. The excess risk for cancers of the digestive system was based on small numbers of cases at a wide variety of sites.]

Henderson *et al.* (1995) further examined the association between cancer of the breast and serum PBB concentration in a case–control study with 1925 women enrolled in the Michigan cohort. Twenty women who developed cancer of the breast were matched on race and age to 290 control women. The risk of cancer of the breast was elevated among women with serum PBB concentrations of 2.0–3.0 ppb (OR, 3.3; 95% CI, 0.8–13), and 4.0 ppb or greater (OR, 3.2; 95% CI, 0.8–13) compared with women with < 2.0 ppb after adjustment for body-mass index (BMI), history of cancer in a female relative, and other risk factors for cancer of the breast. [This study was informative despite its small size, given the paucity of information available on populations exposed to PBBs.]

Wong *et al.* (1984) conducted a mortality study in a historical cohort of white male chemical workers employed between 1935 and 1976. The workers' potential exposure to several chemicals, including PBBs, was categorized as more highly exposed (routine exposure) and less exposed (non-routine exposure). No detailed analysis of PBB exposure was presented. A total of 91 workers were classified as potentially exposed on a routine basis, and none died during the study period; among the 237 non-routinely exposed workers, 2 deaths were observed versus 6.4 expected, one of which was due to cancer of the large intestine (standardized mortality ratio, SMR, 10, [95% CI, 0.3–55]). This case of cancer of the large intestine was observed among 87 people who worked in the research laboratories and were classified as non-routinely exposed to PBBs (SMR, 80.4 [95% CI, 2.53–557]). [The study was uninformative because of the crude exposure classification and the small number of deaths in the PBB-exposed workers.]

3. Cancer in Experimental Animals

PBBs were previously evaluated for carcinogenicity in experimental animals (IARC, 1978, 1986). In the 1978 evaluation, the Working Group determined that there was inadequate evidence to classify PBBs. However, the 1986 evaluation determined that there was *sufficient evidence* in experimental animals for the carcinogenicity of commercial mixtures of PBBs. Since that time, new data had become available, and were taken into account in the present evaluation. Only data from original research have been summarized in the tables.

3.1 Mouse

See Table 3.1

3.1.1 Oral administration

The United States National Toxicology Program (NTP) studied the carcinogenic potential of Firemaster FF-1 (see Section 1 for composition) in mice when administered orally (NTP, 1983). Groups of 50 male and 50 female B6C3F$_1$ mice were given Firemaster FF-1 at a dose of 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg body weight (bw) per day by gavage on five consecutive days per week for 6 months. The mice were then observed for an additional 18 months after treatment, i.e. 24 months in total (lifetime observation). There was a statistically significant increase ($P < 0.01$) in the incidence of hepatocellular carcinoma in males and females at 10 mg/kg bw per day: 21 out of 22 (95%) versus 12 out of 25 (48%; controls) in males; 7 out of 8 (88%) versus 0 out of 13 (controls) in females. The incidence of hepatic neoplasms appeared to be dose-dependent. Liver tumours were observed primarily in those groups of mice to which FF-1 was given in doses sufficient to induce hepatic toxicity. There was a trend towards an increase in the incidence of thyroid follicular cell adenoma in females treated

Table 3.1 Studies of carcinogenicity with PBBs in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Oral administration				
Mouse, $B6C3F_1$ (M, F) 30 mo Gupta *et al.* (1983a), NTP (1983), Silberhorn *et al.* (1990), EFSA (2010)	Firemaster FF-1 at 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg bw per day in corn oil, 5 d/wk, for 25 wk; observed for total of 24 mo 50 mice/group; age 7–8 wk	*Males* Neoplastic nodules: 2/25 (8%), 1/27 (4%), 4/24 (17%), 2/25 (8%), 2/23 (9%), 1/22 (5%) Hepatocellular carcinoma: 12/25 (48%), 8/27 (30%), 8/24 (33%), 12/25 (48%), 15/23 (65%), 21/22 (95%)* *Females* Hepatocellular adenoma: 0/13, 2/19 (11%), 0/15, 1/11 (9%), 1/17 (6%), 1/8 (12%) Hepatocellular carcinoma: 0/13, 0/19, 2/15 (13%), 2/11 (18%), 3/17 (18%), 7/8 (88%)*	*$P < 0.01$ *$P < 0.01$	Firemaster FF-1 blended with 2% calcium trisilicate Hyperplasia/adenoma of the follicular cells of the thyroid was not considered a major finding because of the small sample size and low incidence. Shortened survival time in mice at 10.0 mg/kg bw per day.
Mouse, C57BL/10ScSn (M) 12 mo Smith *et al.* (1990, 1995)	Inferon (iron-dextran): 600 mg/kg, s.c., followed by Firemaster BP-6 in diet [dose, NR] for 2 mo, followed by control diet for 10 mo Group 1: Fe (–) Group 2: Fe (+) Group 3: Fe (–) + Firemaster BP-6 Group 4: Fe (+) + Firemaster BP-6 7–19 mice/group; age 7–10 wks	Hepatocellular carcinoma: 0/15, 0/16, 0/7, 0/7 Hepatocellular nodules: 0/15, 0/16, 1/7 (14%), 4/7 (57%)	NS	Purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Transplacental and perinatal exposure				
Mouse, B6C3F$_1$ (M, F) 2 yr Chhabra *et al.* (1993), NTP (1993)	Perinatal exposure (F$_0$): Firemaster FF-1 at 0, 3, 10, or 30 ppm in feed from 60 d before breeding until weaning of the F$_1$ generation. Adult exposure (F$_1$): F$_1$ given same diet as F$_0$ through gestation, lactation, and 4 wk after weaning (age 8 wk), then diets containing Firemaster FF-1 at 0, 3, 10, or 30 ppm, 7 d/wk for 105 wk F$_0$:F$_1$ – 0:0, 0:10, 0:30 ppm (adult exposure only) F$_0$:F$_1$ – 0:0, 30:0 ppm (perinatal exposure only) F$_0$:F$_1$ – 0:10, 10:10, 30:10 ppm (perinatal plus adult exposure) F$_0$:F$_1$ – 0:30, 30:30 ppm (perinatal plus adult exposure) 60 mice/group	**F$_0$:F$_1$ – 0:0, 0:10, 0:30 ppm (adult exposure only)** *Males* Hepatocellular adenoma: 9/50 (18%), 48/49 (98%)*, 42/50 (84%)* Hepatocellular carcinoma: 8/50 (16%), 30/49 (61%)*, 36/50 (72%)* Hepatocellular adenoma or carcinoma (combined): 16/50 (32%), 48/49 (98%)*, 48/50 (96%)* *Females* Hepatocellular adenoma: 4/50 (8%), 39/50 (78%)*, 46/48 (96%)* Hepatocellular carcinoma: 1/50 (2%), 22/50 (44%)*, 35/48 (73%)* Hepatocellular adenoma or carcinoma (combined): 5/50 (10%), 42/50 (84%)*, 47/48 (98%)* **F$_0$:F$_1$ – 0:0, 30:0 ppm (perinatal exposure only)** *Males* Hepatocellular adenoma: 9/50 (18%), 31/50 (62%) Hepatocellular carcinoma: 8/50 (16%), 17/50 (34%) Hepatocellular adenoma or carcinoma (combined): 16/50 (32%), 40/50 (80%)	*$P < 0.001$ $P < 0.001$ (trend) *$P < 0.001$ $P < 0.001$ (trend) *$P < 0.001$ $P < 0.0001$ (trend) *$P < 0.001$ $P < 0.001$ (trend) *$P < 0.001$ $P < 0.001$ (trend) *$P < 0.001$ $P < 0.001$ (trend) $P < 0.001$ $P = 0.03$ $P < 0.001$	Purity, NR All mice at 0:30 or 30:30 ppm died before the end of the study. The survival of females at 30:10 ppm was lower than that of controls. Survival of males at 3:3 ppm was greater than that of controls. Other microscopic changes included hepatocyte cytomegaly, fatty change, clear cell focus, eosinophilic focus, hepatocyte necrosis, bile duct hyperplasia and hepatocyte cytological alteration.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		*Females*		
		Hepatocellular adenoma: 4/50 (8%), 19/50 (38%)	$P < 0.001$	
		Hepatocellular carcinoma: 1/50 (2%), 4/50 (8%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 5/50 (10%), 21/50 (42%)	$P < 0.001$	
		F$_0$:F$_1$ – 0:10, 10:10, 30:10 ppm (perinatal + adult exposure)	**Effect of perinatal exposure on the effect of adult exposure at 10 ppm (compared with 0:10)**	
		Males		
		Hepatocellular adenoma: 48/49 (98%), 46/49 (94%), 48/50 (96%)	NS	
		Hepatocellular carcinoma: 30/49 (61%), 31/49 (63%), 40/50 (80%)*	*$P = 0.01$	
		Hepatocellular adenoma or carcinoma (combined): 48/50 (98%), 46/49 (94%), 48/50 (96%)	NS	
		Thyroid follicular cell adenoma: 0/49, 0/48, 5/48 (10%)*	*$P = 0.02$ $P = 0.003$ (trend)	
		Females		
		Hepatocellular adenoma: 39/50 (78%), 38/50 (76%), 47/50 (94%)*	*$P = 0.005$ $P < 0.001$ (trend)	
		Hepatocellular carcinoma: 22/50 (44%), 26/50 (52%), 44/50 (88%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular adenoma or carcinoma (combined): 42/50 (84%), 44/50 (88%), 50/50 (100%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Thyroid follicular cell adenoma: 1/50 (2%), 1/50 (2%), 2/50 (4%)	NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		**F_0:F_1 – 0:30, 30:30 ppm (perinatal + adult exposure)**	**Effect of perinatal exposure on adult exposure at 30 ppm (compared with 0:30)**	
		Males		
		Hepatocellular adenoma: 42/50 (84%), 48/50 (96%)	$P = 0.007$	
		Hepatocellular carcinoma: 36/50 (72%), 35/50 (70%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 48/50 (96%), 50/50 (100%)	NS	
		Females		
		Hepatocellular adenoma: 46/48 (96%), 41/47 (87%)	NS	
		Hepatocellular carcinoma: 35/48 (73%), 29/47 (62%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 47/48 (98%), 47/47 (100%)	NS	
Initiation–promotion				
Mouse, CD1 (F) 30 wk Berry *et al.* (1978, 1979)	Initiated with topical application of 200 nmol DMBA in acetone. After 1 wk, mice received 2 µg TPA, or 100 µg Firemaster BP-6, 2×/wk for 30 wk Groups: DMBA only TPA only DMBA + TPA DMBA + Firemaster BP-6 Firemaster BP-6 only 30 mice/group; age 6–8 wks	Skin papilloma: 0/30, 1/30 (3%), 28/30 (93%), 0/30, 0/30		Purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, HRS/1 hairless (F) 20 wk Poland *et al.* (1982)	Mice (age 8 weeks) initiated with a single dose of MNNG (5 µmol in 50 µL of acetone) or vehicle applied to the dorsal skin, then 2 mg of Firemaster FF-1 (in 50 µL of acetone), 2×/wk for 5 wk, then 1 mg for 15 wk; PBB-153 or PBB-169, 20 µg in 50 µL of acetone 2×/wk topically for 20 wk. MNNG + FF-1, PBB-153-only, and MNNG-only groups: 26 mice/group MNNG + PBB-153, MNNG + PBB-169, PBB-169-only, and FF-1-only groups: 20 mice/group	Skin papilloma: MNNG only: 0/23 (0) MNNG + FF-1: 9/15 (60%)* (2.0)* MNNG + PBB-153: 0/20 MNNG + PBB-169: 12/20 (60%)* × (1.5)* FF-1 only: 1/16 (6%) (0.13) PBB-153 only: 0/22 PBB-169 only: 0/20	* Significant increase in incidence or multiplicity	Purity, NR Statistical analysis, NR

bw, body weight; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; M, male; MNNG, *N*-methyl-*N*′-nitro-*N*-nitroguanine; mo, month; NR, not reported; NS, not significant; PBBs, polybrominated biphenyls; s.c., subcutaneous; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week

with FF-1, but the incidences were low and the numbers of animals were small.

Groups of 7–19 male Ah-responsive C57BL/10ScSn mice received a single dose of iron-dextran (600 mg/kg) and were then fed a diet containing Firemaster BP-6 [dose not reported] for 2 months, followed by the control diet for 10 months. Hepatocellular nodules were observed in one mouse given Firemaster BP-6 only. Pre-treatment with iron-dextran did not have a significant synergistic effect on the induction of hepatocellular tumours (Smith *et al.*, 1990). [The limitations of the study precluded its use in the evaluation process.]

3.1.2 Transplacental and perinatal exposure

The NTP conducted studies of carcinogenicity in male and female B6C3F_1 mice given diets containing PBBs (Firemaster FF-1) to determine: (i) the effects of PBBs in mice receiving adult (F_1) exposure only from age 8 weeks for 2 years [conventional study of carcinogenicity]; (ii) perinatal (F_0) exposure only (dietary exposure of dams before breeding, and throughout gestation and lactation) followed by control diet for 2 years; and (iii) the combined effect of perinatal and adult exposure (Chhabra *et al.*, 1993; NTP, 1993).

Groups of 60 female mice were exposed to Firemaster FF-1 at a dietary concentration of 0, 3, 10, or 30 ppm for 60 days before breeding. After breeding to previously unexposed males, exposure continued throughout pregnancy and lactation. Weaning occurred on postnatal day 28, and dietary exposure at these same concentrations continued until the pups were approximately age 8 weeks. Subsequently, groups of 60 male and 60 female pups (F_1) were given Firemaster FF-1 at the same dietary concentrations (0, 3, 10, or 30 ppm) and continued on these diets for up to 2 years. After 9 months, 10 mice per group were evaluated.

At 9 months, hepatocellular adenomas occurred in one or more male and female mice from each exposure group, with a significant increase in incidence in the group at 30:30 ppm. A hepatocellular carcinoma occurred in one female mouse in the group at 30:30 ppm.

After 2 years, the effect of adult exposure [conventional study of carcinogenicity] was determined by comparing the groups at 0:0, 0:10 and 0:30 ppm. The incidences of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) were significantly increased ($P \leq 0.01$) in mice at 0:10 and 0:30 ppm. While a single hepatocellular adenoma or carcinoma occurred in tumour-bearing control mice, multiple adenomas, carcinomas, or both adenomas and carcinomas were often present in exposed mice. The effects of perinatal exposure only were determined by comparing the groups at 0:0 and 30:0 ppm. The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased ($P \leq 0.001$) in mice at 30:0 ppm. The effects of perinatal exposure plus adult exposure were determined by comparing the groups at 0:10, 10:10 and 30:10 ppm, and the groups at 0:30 and 30:30 ppm. When mice were exposed to the lower adult dose, there was a significant increase in the incidence of hepatocellular adenoma and carcinoma in females, and of carcinoma in males (Chhabra *et al.*, 1993; NTP, 1993).

3.1.3 Initiation–promotion

In an initiation–promotion study, groups of 30 female CD1 mice were initiated with a skin application of 200 nmol of 7,12-dimethylbenz[*a*]anthracene (DMBA) in acetone, or acetone only. One week later, the mice received topical applications of 2 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) or 100 µg of Firemaster-BP6 in acetone, twice per week for 30 weeks. Firemaster-BP6 alone did not induce or promote

DMBA-initiated skin tumours (Berry *et al.*, 1978; Berry *et al.*, 1979).

Poland *et al.* (1982) investigated whether Firemaster FF-1 could promote *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)-initiated skin tumours in female HRS/1 hairless mice, as part of a larger study examining the skin tumour-promoting activity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), PCBs, and polychlorinated dibenzofurans (PCDFs). At age 8 weeks, mice were given a single topical dose of MNNG (5 µmol in 50 µL of acetone), or the vehicle only. Mice were then given a topical dose of Firemaster FF-1 (2 mg in 50 µL of acetone) twice per week for 5 weeks, then 1 mg for 15 weeks; or 2,2′,4,4′,5,5′-hexabromobiphenyl (PBB-153) or 3,3′,4,4′,5,5′-hexabromobiphenyl (PBB-169), 20 µg or 50 µL of acetone, respectively, twice per week for 20 weeks. There were 26 mice in the MNNG + FF-1, PBB-153-only, and MNNG-only groups; and 20 mice in the MNNG + PBB-153, MNNG + PBB-169, PBB-169-only, and FF-1 only groups. Tumours were classified as skin papillomas. Firemaster FF-1 and PBB-169 increased the incidence and multiplicity of MNNG-initiated tumours. [Statistical analysis was not reported.]

3.2 Rat

See Table 3.2

3.2.1 Oral administration

The NTP studied the carcinogenic potential of PBBs when administered orally in rats (NTP, 1983). Groups of 50 male and female Fischer F344 rats were given Firemaster FF-1 at a dose of 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg bw per day by gavage on five consecutive days per week for 6 months. The rats were then observed for an additional 24 months (lifetime observation). The incidence of hepatocellular carcinoma was significantly increased ($P < 0.01$) in males and females at 10 mg/kg bw per day – males, 7 out of 31 (23%) versus 0 out of 33 (controls), and females, 7 out of 20 (35%) versus 0 out of 20 (controls) – and in males at 3 mg/kg bw per day – 7 out of 33 (21%) versus 0 out of 33 (controls). There was also a significant increase ($P < 0.01$) in the incidence of cholangiocarcinoma in females at 10 mg/kg bw per day – 7 out of 20 (35%) versus 0 out of 21 (controls) – and a slight increase ($P = 0.06$) in males at 10 mg/kg bw per day – 2 out of 31 (6%) versus 0 out of 33 (controls). The incidences of hepatic neoplastic nodules in female rats at 3 mg/kg bw per day and higher were significantly increased ($P < 0.01$). There was no clear effect of treatment on the incidence of hepatic neoplastic nodules in males. Liver tumours were observed primarily in rats to which Firemaster FF-1 was given in doses sufficient to induce hepatic toxicity. An increased incidence of myelomonocytic leukaemia was also observed in male rats at 0.3 mg/kg bw per day. [The Working Group noted that the spectrum of neoplastic lesions in the liver was similar to that associated with exposure to PCB-126 and PCB-118 in NTP studies, and hypothesized that the effect observed could be due to PCB activity or the presence of impurities that had dioxin-like activity.]

In a series of studies, Kimbrough *et al.* (1981) dosed non-inbred female Sherman rats with Firemaster FF-1. In one study, groups of 65 female rats were given a single dose of PBBs at 1000 mg/kg bw by gavage and observed for 24 months. The incidence of hepatocellular (trabecular) carcinoma and hepatic neoplastic nodules [adenomas] was significantly increased – 24 out of 58 (41%) versus 0 out of 53 (controls) and 42 out of 58 (72%) versus 0 out of 53 (controls), respectively. In a second study, groups of 30 female rats were given Firemaster FF-1 at a dose of 100 mg/kg bw by gavage twice per week for two 3-week periods separated by approximately 10 weeks (total of 12 doses). After 24 months observation, the incidences of hepatocellular (trabecular) carcinoma and hepatic neoplastic nodules were significantly increased – 17 out of

Table 3.2 Studies of carcinogenicity with PBBs in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344/N (M, F) 29 mo Gupta *et al.* (1983a), NTP (1983), Silberhorn *et al.* (1990), EFSA (2010)	Firemaster FF-1 at 0 (corn oil), 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg bw per day, 5 d/wk by gavage for up to 25 wk, and then observed for 23 mo without exposure 51 rats/group; age 7–8 wk	*Males* Neoplastic nodules: 0/33, 0/39, 1/40 (2%), 4/31 (13%)*, 4/33 (12%), 1/31 (3%) Hepatocellular carcinoma: 0/33, 2/39 (5%), 0/40, 1/33 (3%), 7/33 (21%)*, 7/31 (23%)* Cholangiocarcinoma: 0/33, 0/39, 0/40, 0/31, 0/33, 2/31 (6%)* Myelomonocytic leukaemia: 3/33 (9%), 5/39 (13%), 8/40 (20%)*, 4/31 (13%), 2/33 (6%), 2/32 (6%) *Females* Neoplastic nodules: 0/20, 2/21 (10%), 0/21, 2/11 (18%), 5/19 (26%)*, 8/20 (40%)* Hepatocellular carcinoma: 0/20, 0/21, 0/21, 0/11, 3/19 (16%), 7/20 (35%)* Cholangiocarcinoma: 0/20, 0/21, 0/21, 0/11, 0/19, 7/20 (35%)* Myelomonocytic leukaemia: 5/20 (25%), 4/21 (19%), 4/21 (19%), 1/11 (9%), 2/19 (11%), 4/20 (20%)	*$P < 0.05$ *$P < 0.01$ *$P = 0.06$ $P < 0.01$ (trend) *$P < 0.05$ *$P < 0.01$ $P < 0.01$ (trend) *$P < 0.01$ $P < 0.01$ (trend) *$P < 0.01$ $P < 0.01$ (trend) NS	Purity, NR Dose-dependent decrease in survival in males; survival in males at ≥ 0.3 mg/kg bw was significantly less ($P < 0.01$) than controls. Other microscopic lesions included atypical foci and bile duct hyperplasia in liver. [The Working Group noted that the same spectrum of neoplastic lesions in the liver was seen in a long-term NTP study using PCB-126 or PCB-118 (see Section 3, *Monograph* on Polychlorinated Biphenyls in this Volume).]
Rat, Sherman (F) Study I: 23 mo Study II: 24 mo Study III: 22 mo Kimbrough *et al.* (1981), Silberhorn *et al.* (1990), EFSA (2010)	*Study I:* Single dose of 1000 mg/kg bw Firemaster FF-1 or corn oil (control); 65 rats/group; age 2 mo *Study II:* corn oil (control), or 100 mg/kg bw Firemaster FF-1 2×/wk every 3 wk, total of 12 doses; 30 rats/group; age 2 mo *Study III:* Single dose of 200 mg/kg bw Firemaster FF-1 or corn oil (control); 16 rats/group; age 4 mo	*Study I* Liver Trabecular carcinoma: 0/53, 24/58 (41%) Neoplastic nodules: 0/53, 42/58 (72%) *Study II* Liver Trabecular carcinoma: 0/25, 17/28 (61%)	 $P < 0.001$ $P < 0.001$ $P < 0.001$	Other non-neoplastic lesions included altered areas or foci, adenofibrosis and multinucleated hepatocytes in liver. Histological description of the neoplastic nodules was consistent with hepatocellular adenoma.

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sherman (F) Study I: 23 mo Study II: 24 mo Study III: 22 mo Kimbrough et al. (1981), Silberhorn et al. (1990), EFSA (2010) cont.)		Neoplastic nodules: 1/25 (4%), 24/28 (82%)	$P < 0.001$	
		Adenocarcinoma: 0/25, 1/28 (4%)	NS	
		Haemangioma: 1/25 (4%), 0/28	NS	
		Total malignant tumours: 0/25, 19/28 (68%)	$P < 0.001$	
		Study III		
		Liver: neoplastic nodules: 0/19, 5/16 (31%)	$P = 0.013$	
Transplacental and perinatal exposure				
Rat, F344/N (M, F) 2 yr Chhabra *et al.* (1993), NTP (1993)	Perinatal exposure (F_0): Firemaster FF-1 at 0, 1, 3, 10 ppm in feed from 60 d before breeding until weaning of the F_1 generation. Adult exposure (F_1): same diet as F_0 during gestation, lactation, and for 4 wk after weaning (age 8 wk); then FF-1 at 0, 3, 10, or 30 ppm, 7 d/wk for 104 wk. 60 rats/group F_0:F_1 – 0:0, 0:10, 0:30 ppm (adult exposure only) F_0:F_1 – 0:0, 10:0 ppm (perinatal exposure only) F_0:F_1 – 0:10, 3:10, 10:10 ppm (perinatal plus adult exposure) F_0:F_1 – 0:30, 10:30 ppm (perinatal plus adult exposure)	**F_0:F_1 – 0:0, 0:10, 0:30 ppm (adult exposure only)** *Males* Hepatocellular adenoma: 1/50 (2%), 10/49 (20%), 38/50 (76%)	$P = 0.002$ (0:10) $P < 0.001$ (0:30) $P < 0.001$ (trend)	Purity, NR Other microscopic changes included hepatocyte hypertrophy, eosinophilic focus, oval cell hyperplasia, hepatocyte cytoplasmic vacuolation and bile duct fibrosis.
		Hepatocellular carcinoma: 0/50, 2/49 (4%), 19/50 (38%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Hepatocellular adenoma or carcinoma (combined): 1/50 (2%), 12/49 (24%)*, 41/50 (82%)*	*$P < 0.001$ $P < 0.001$ (trend)	
		Females Hepatocellular adenoma: 0/50, 10/50 (20%), 38/50 (76%)	$P = 0.001$ (0:10) $P < 0.001$ (0:30) $P < 0.001$ (trend)	
		Hepatocellular carcinoma: 0/50, 2/50 (4%), 4/50 (8%)	NS	
		Hepatocellular adenoma or carcinoma (combined): 0/50, 12/50 (24%)*, 39/50 (78%)*	*$P < 0.001$ $P < 0.001$ (trend)	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344/N (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		**F_0:F_1 – 0:0, 10:0 ppm (perinatal exposure only)**		
		Males		
		Hepatocellular adenoma: 1/50 (2%), 5/50 (10%)	NS	
		Females		
		Hepatocellular adenoma: 0/50, 0/50	NS	
		F_0:F_1 – 0:0, 0:10, 3:10, 10:10 ppm (perinatal plus adult exposure)	**Effect of perinatal exposure on the effect of adult exposure at 10 ppm (compared to 0:10)**	**Effect of total exposure on carcinogenicity (compared to 0:0)**
		Males		
		Hepatocellular adenoma: 1/50 (2%), 10/49 (20%), 13/50 (26%), 16/50 (32%)	NS	[$P < 0.01$ (3:10 and 10:10)]
		Hepatocellular carcinoma: 0/50, 2/49 (4%), 1/50 (2%), 1/50 (2%)	NS	NS
		Hepatocellular adenoma or carcinoma (combined): 1/50 (2%), 12/49 (24%), 14/50 (28%), 16/50 (32%)	NS	$P < 0.001$ (0:10, 3:10, 10:10)
		Females		
		Hepatocellular adenoma: 0/50, 10/50 (20%), 22/50 (44%), 35/50 (70%)	$P < 0.001$ (10:10)	$P < 0.001$ (0:10 and [3:10]) [$P < 0.0001$ (10:10)] [$P < 0.001$ (trend)]
		Hepatocellular carcinoma: 0/50, 2/50 (4%), 1/50 (2%), 8/50 (16%)	$P < 0.01$ (10:10)	[$P < 0.005$ (10:10)]
		Hepatocellular adenoma or carcinoma (combined): 0/50, 12/50 (24%), 22/50 (44%), 39/50 (78%)	$P = 0.03$ (3:10) $P < 0.001$ (10:10) $P < 0.001$ (trend)	$P < 0.001$ (0:10; 3:10; 10:10) [$P < 0.001$ (trend)]

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344/N (M, F) 2 yr Chhabra et al. (1993), NTP (1993) (cont.)		**F_0:F_1 – 0:0, 0:30, 10:30 ppm (perinatal plus adult exposure)**	**Effect of perinatal exposure on the effect of adult exposure at 30 ppm (compared with 0:30)**	**Effect of total exposure on carcinogenicity (compared with 0:0)**
		Males		
		Hepatocellular adenoma: 1/50 (2%), 38/50 (76%), 38/50 (76%)	NS	$P < 0.001$ (0:30 and [10:30])
		Hepatocellular carcinoma: 0/50, 19/50 (38%), 23/50 (46%)	NS	$P < 0.001$ (0:30 and [10:30])
		Hepatocellular adenoma or carcinoma (combined): 1/50, 41/50 (82%), 41/50 (82%)	NS	$P < 0.001$ (0:30 and 10:30)
		Females		
		Hepatocellular adenoma: 0/50, 38/50 (76%), 45/50 (90%)	NS	$P < 0.001$ (0:30) [$P < 0.0001$ (10:30)]
		Hepatocellular carcinoma: 0/50, 4/50 (8%), 22/50 (44%)	$P < 0.001$	[$P < 0.0001$ (10:30)]
		Hepatocellular adenoma or carcinoma (combined): 0/50, 39/50 (78%), 47/50 (94%)	$P < 0.05$	$P < 0.001$ (0:30 and 10:30)
Rat, Sherman (M, F) 24 mo Groce & Kimbrough (1984), EFSA (2010)	Pregnant females given corn oil or Firemaster FF-1 (200 mg/kg bw in corn oil) by gavage on d 7 and d 14 of pregnancy. Weaned pups (exposure through placenta and milk) assigned to: Approximately 50 pups/group	*Males*		Purity, NR Other recorded non-neoplastic lesions included foci or altered areas in liver, hepatic cysts, chronic nephrosclerosis, chronic nephritis, interstitial fibrosis and adenomatous hyperplasia in lung and testicular atrophy in males; and foci or altered areas and adenofibrosis in liver, cardiac interstitial fibrosis, chronic nephrosclerosis, interstitial fibrosis in lung, endometrial polyp and ovarian cyst in females.
		Hepatocellular (trabecular) carcinoma: 0/42, 4/41 (10%)	NS	
		Neoplastic nodules: 0/42, 2/41 (5%)	NS	
		Females		
		Hepatocellular trabecular carcinoma: 0/48, 3/51 (6%)	NS	
		Neoplastic nodules: 2/48 (4%), 9/51 (18%)	NS	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Initiation–promotion				
Rat, Sprague Dawley (F) 180 d Jensen *et al.* (1982), EFSA (2010)	Rats given NDEA at 10 mg/kg bw i.p., 24 h after partial hepatectomy (PH); then 30 d later fed diets containing PB at 500 ppm, or Firemaster BP-6, or PBB-153 at 10 or 100 ppm for 180 d. Controls included rats without PH or NDEA, but fed the same diets. Group 1: PH + NDEA Group 2: None Group 3: PH + NDEA + PB Group 4: PH + NDEA + 10 ppm PBB-153 Group 5: None + 10 ppm PBB-153 Group 6: PH + NDEA + 100 ppm PBB-153 Group 7: None + 100 ppm PBB-153 Group 8: PH + NDEA + 10 ppm BP-6 Group 9: None + 10 ppm BP-6 Group 10: PH + NDEA + 100 ppm BP-6 Group 11: None + 100 ppm BP-6 Three or six/group	Liver neoplastic nodules: 0/6, 0/3, 2/6 (33%), 3/6 (50%), 0/3, 5/6 (83%), 1/3 (33%), 6/6 (100%), 0/3, 6/6 (100%), 2/3 (66%)	$P < 0.05$ (groups 6, 8 and 10 vs group 1)	BP-6 purity, NR; PBB-153 purity, > 99.9% Rats given BP-6 or PBB-153 without PH or NDEA had few altered foci compared with those given PH or NDEA. PBB-153 increased the number of enzyme-altered foci. Limitations of the study included small number of rats and short duration (i.e. less than lifetime exposure).
Rat, Sprague Dawley (F) 480 d Jensen & Sleight (1986), EFSA (2010)	Single dose of NDEA at 10 mg/kg bw, 24 h after partial hepatectomy (PH); 30 d later given 0.1 mg PBB-153 or PBB-169 for 140 d, then basal diet for another 310 d Group 1: Basal diet Group 2: PH + NDEA Group 3: PBB-169 Group 4: PH + NDEA + PBB-169 Group 5: PBB-153 Group 6: PH + NDEA + PBB-153 Group 7: PBB-153 + PBB-169 Group 8: PH + NDEA + PBB-153 + PBB-169 6–12 rats/group	*All groups* Hepatocellular carcinoma: 0/6, 0/12, 0/6, 1/11 (9%), 0/6, 1/10 (10%), 0/6, 1/11 (9%) Hepatocellular nodules: 0, 0.11, 0, 0.25, 0, 1.94, 0, 3.85	$P < 0.05$ (group 6 and group 8)	PBB-153 purity, > 99%; PBB-169 purity, > 99% The combination of PBB-153 and PBB-169 caused a synergistic effect on the development of altered hepatic foci and hepatic nodules per cm^3 liver.

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence, (%) and/or multiplicity of tumours	Significance	Comments
Administration with known carcinogens				
Rat, Sprague Dawley (F) 57 wk Schwartz *et al.* (1980)	Firemaster BP-6 at 50 ppm; after 4 wk, AAF added at 300 ppm for up to 57 wk. Group 1: Basal diet Group 2: BP-6 Group 3: AAF Group 4: BP-6 + AAF 8 or 12 rats/group; age at start, NR	Hepatocellular carcinoma: 0/8, 0/12, 3/8 (37%), 5/12 (42%) Cholangiocarcinoma: 0/8, 0/12, 1/8 (12%), 0/12 Mixed liver carcinoma: 0/8, 0/12, 1/8 (12%), 0/12 Mammary gland, adenocarcinoma: 0/8, 1/12 (8%), 3/8 (37%), 0/12 Mammary gland, cystadenocarcinoma: 0/8, 0/12, 4/8 (50%), 2/12 (17%) Ear duct gland, squamous cell carcinoma: 0/8, 0/12, 5/8 (62%), 1/12 (8%) Lung (metastatic tumours): 0/8, 0/12, 1/8 (12%), 1/12 (8%)		Purity of AAF and BP-6, NR Small numbers of rats and short observation period.

AAF, 2-acetylaminofluorene; bw, body weight; d, day; F, female; h, hour; M, male; MCL, mononuclear cell leukaemia; mo, month; NDEA, *N*-nitrosodiethylamine; NR, not reported; PBBs, polybrominated biphenyls; PH, partial hepatectomy; wk, week; yr, year

28 (61%) versus 0 out of 25 (controls), and 24 out of 28 (82%) versus 1 out of 25 (4%; controls). In a third study, groups of 16 female rats were given Firemaster FF-1 as a single dose at 200 mg/kg bw by gavage. After 22 months, the incidence of hepatic neoplastic nodules was significantly increased – 5 out of 16 (31%) versus 0 out of 19 (controls).

3.2.2 Transplacental and perinatal exposure

The NTP conducted long-term studies of toxicity and carcinogenicity in male and female F344/N rats given diets containing PBBs (Firemaster FF-1) to determine: (i) the effects of PBBs in rats receiving adult (F_1) exposure only from age 8 weeks for 2 years [conventional study of carcinogenicity]; (ii) perinatal (F_0) exposure only (dietary exposure of dams before breeding and throughout gestation and lactation) followed by control diet for 2 years; and (iii) the combined effects of perinatal and adult exposure (Chhabra *et al.*, 1993; NTP, 1993).

Groups of 60 female rats were exposed to Firemaster FF-1 at a dietary concentration of 0, 1, 3, or 10 ppm for 60 days before breeding. After breeding to previously unexposed males, exposure continued throughout pregnancy and lactation. Weaning occurred on postnatal day 28, and dietary exposure at these same concentrations continued until the pups were approximately age 8 weeks. Subsequently, groups of 60 male and 60 female pups (F_1) were given Firemaster FF-1 at the same dietary concentrations (0, 3, 10, or 30 ppm) and continued on these diets for up to 2 years.

After 2 years, the effects of adult exposure [conventional study of carcinogenicity] were determined by comparing the groups at 0:0, 0:10 and 0:30 ppm. The incidences of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined) were all significantly increased in males and females of the groups at 0:10 and 0:30 ppm. The majority of male and female rats had multiple hepatocellular adenomas. The incidence of hepatocellular carcinoma was significantly increased in males at 0:30 ppm. Although the combined incidence of adenoma and carcinoma was similar for males and females, there were more carcinomas in males at 0:30 ppm (19 carcinomas) than in females (4 carcinomas). Multiple hepatocellular carcinomas occurred in seven males at 0:30 ppm. In the perinatal-only exposure study, the neoplastic effects of perinatal exposure were determined by comparing the groups at 0:0 and 10:0 ppm; marginal increases in the incidence of hepatocellular adenoma (1 out of 50, 5 out of 50) were noted in males. The effects of perinatal exposure plus adult exposure were determined by comparing the groups at 0:10, 3:10, and 10:10 ppm, and the groups at 0:30 and 10:30 ppm. The incidence of hepatic tumours in females was significantly greater than in those rats exposed only as adults. In females receiving varying concentrations at F_0 and a constant concentration of 10 or 30 ppm at F_1, the incidences of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined), increased significantly with the concentration given at F_0. The incidence of mononuclear cell leukaemia in males and females in the groups exposed either as adults only or both perinatally and as adults generally was significantly elevated compared with untreated controls, most notably at the higher exposures (Chhabra *et al.*, 1993; NTP, 1993).

In a study in pregnant Sherman rats given Firemaster FF-1 at an oral dose of 200 mg/kg bw on days 7 and 14 of gestation, the incidences of neoplastic nodules and hepatocellular carcinoma were slightly increased (not significantly) in male and female offspring over the 24 months after treatment (Groce & Kimbrough, 1984).

3.2.3 Initiation–promotion

To determine whether PBB mixtures or individual congeners could serve as tumour promoters in a two-stage test for hepatocarcinogenesis, groups of three or six female Sprague-Dawley rats were given *N*-nitrosodiethylamine (NDEA) as a single intraperitoneal dose at 10 mg/kg bw, 24 hours after a 70% partial hepatectomy. After 30 days, the rats were fed a basal diet or a basal diet containing Firemaster BP-6 or PBB-153 [called "HBB" in the article] at a concentration of 10 or 100 ppm for 180 days. Diets were prepared by adding phenobarbital, Firemaster BP-6 or PBB-153 in corn oil to a basal diet. Controls included non-hepatectomized rats or rats not given NDEA. At 100 ppm, Firemaster BP-6 alone caused an increase (two out of three rats; not statistically significant) in the incidence of neoplastic nodules. In combination with partial hepatectomy and NDEA, diets that contained Firemaster BP-6 or PBB-153 were associated with significant ($P < 0.05$) promotion of neoplastic nodules: five out of six rats receiving PBB-153 at 100 ppm, and six out of six rats receiving Firemaster BP-6 at 10 ppm, and six out of six rats receiving Firemaster BP-6 at 100 ppm. Both Firemaster BP-6 and PBB-153 increased the number of enzyme-altered foci (Jensen *et al.*, 1982). [The limited numbers of animals and less-than-lifetime observation period in this study limited the conclusions that could be reached on carcinogenic potential.]

To determine the effect of individual PBB congeners on the enhancement of gamma-glutamyl transpeptidase (GGT)-positive altered hepatic foci and the development of hepatic nodules and carcinomas, groups of 6 or 12 female Sprague-Dawley rats were given a single dose of NDEA, 24 hours after a 70% partial hepatectomy. After 30 days, the rats were fed a basal diet, or the basal diet containing PBB-153 at 10 ppm, PBB-169 at 0.1 ppm, or PBB-153 (10 ppm) + PBB-169 (0.1 ppm) for 140 days, followed by basal diet for an additional 310 days. Rats were killed 170, 240 or 480 days after partial hepatectomy. Dietary exposure to the PBB congeners alone or in combination did not increase the incidence of hepatocellular carcinoma, hepatic nodules, or altered hepatic foci. However, PBB-153 alone or in combination with PBB-169 increased the development of altered hepatic foci and nodules in partially hepatectomized rats given NDEA. Rats that had not been hepatectomized and given NDEA, and that were fed the basal diet or the basal diet containing PBB congeners, had no or relatively few altered hepatic foci when compared with rats that received the same diets but had been partially hepatectomized and given NDEA (Jensen & Sleight, 1986).

3.2.4 Administration with known carcinogens

Groups of 8 or 12 female Sprague-Dawley rats were given diets containing 2-acetylaminofluorene (AAF) at a concentration of 300 ppm, Firemaster BP-6 at 50 ppm, or BP-6 + AAF, for approximately 1 year. Firemaster BP-6 significantly reduced the incidence of AAF-induced tumours at non-hepatic locations (mammary gland and ear duct), but did not affect the incidence of hepatic tumours. Ingestion of Firemaster BP-6 only did not increase the incidence of tumours when compared with untreated controls (Schwartz *et al.*, 1980). [Conclusions regarding the carcinogenic potential of Firemaster BP-6 were limited by the low number of animals per group and the less-than-lifetime observation period.]

3.3 Hamster

See Table 3.3

Table 3.3 Studies of carcinogenicity with PBBs in hamsters

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Hamster, Syrian Golden (M) 273 d Wasito & Sleight (1989)	Initiated with NDEA as a single s.c. dose at 0 or 80 mg/kg bw, then fed diets containing BP-6 at 0 or 100 mg/kg for 140 days, after which basal diet was given until the end of the study W(d 273). Group 1: control Group 2: NDEA Group 3: NDEA + BP-6 Group 4: BP-6 30 hamsters/group	*Nasal cavity* Papilloma: 0/30, 1/30 (3%), 9/30 (30%), 0/30 Adenoma: 0/30, 2/30 (7%), 1/30 (3%), 0/30 Adenocarcinoma: 0/30, 7/30 (23%), 2/30 (7%), 0/30 Squamous cell carcinoma: 0/30, 0/30, 2/30 (7%), 1/30 (3%) Total nasal tumours: 0/30, 11/30 (37%), 15/30 (50%), 1/30 (3%) *Tracheal papilloma (multiplicity)*: 0, 26, 27, 0 (4.33, 1.6)	$P < 0.05$	Purity, NR Nasal tumours occurred at approximately the same incidence in hamsters given NDEA as in those given NDEA + BP-6.

bw, body weight; d, day; M, male; NDEA, *N*-nitrosodiethylamine; PBBs, polybrominated biphenyls; s.c., subcutaneous

Initiation–promotion

In an initiation–promotion study of carcinogenesis of the respiratory tract, groups of 30 male Syrian Golden hamsters were initiated with a single subcutaneous dose of NDEA at 0 or 80 mg/kg bw and were then (7 days later) fed a diet containing Firemaster BP-6 at 0 or 100 mg/kg for 140 days, followed by basal diet from day 140 until the end of the experiment at 273 days. Firemaster BP-6 slightly promoted the development of benign tracheal papilloma in hamsters. The multiplicity of tracheal papillomas, but not the incidence, was significantly increased in hamsters given NDEA + BP-6 compared with those given NDEA only. Tracheal papilloma was not seen in untreated hamsters or in hamsters fed a diet containing Firemaster BP-6 only. Nasal tumours (total) occurred at approximately the same incidence in hamsters given NDEA only or NDEA + BP-6. Adenomas occurred in the nasal cavity of two hamsters given NDEA only and in one hamster given NDEA + BP-6. Adenocarcinoma occurred in the nasal cavity of seven hamsters given NDEA only, and in two hamsters given NDEA + BP-6. Squamous cell carcinoma of the nasal cavity occurred in two hamsters given NDEA + PBBs and in one hamster given Firemaster BP-6 only (Wasito & Sleight, 1989).

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

PBBs share several chemical and physical characteristics with their chlorinated analogues, including effective absorption and distribution, the higher brominated biphenyls distributing/re-distributing to fatty tissues. PBBs readily cross the placenta in several species (DiCarlo *et al.*, 1978; Ecobichon *et al.*, 1983). PBBs have estimated long half-lives in animal tissues, serum, and fat, ranging from 22 days to more than 69 weeks (Miceli & Marks, 1981; Ecobichon *et al.*, 1983), extending to years in humans (ATSDR, 2004). PBBs have the potential to greatly alter their own distribution, metabolism, and

excretion through at least two mechanisms: PBB congeners are potent and efficacious inducers of xenobiotic-metabolizing enzymes, for which they may also become substrates and inhibitors (see Section 4.3).

4.2 Genetic and related effects

Limited data on PBBs and genotoxicity were available to the Working Group (reviewed in Silberhorn *et al.*, 1990). Firemaster BP-6, Firemaster FF-1, and the individual congeners PBB-77, -153, -169, and -153 + -180 have been tested in assays for genotoxicity. All assays with commercial PBB mixtures or individual congeners gave negative results for genotoxicity in mammals, except one in which a more-than-additive mitotic arrest response was seen in the bone marrow of pregnant rats treated with Firemaster [not further specified] and colchine (Ficsor & Wertz, 1976).

Only three PBB congeners have been tested in bacterial assays for mutation (Silberhorn *et al.*, 1990), i.e. the 2-, 3-, and 4-bromobiphenyls (PBB-1, PBB-2, PBB-3). All results were negative with and without metabolic activation (Haworth *et al.*, 1983), except PBB-3 that gave positive results with activation from S9 (Kohli *et al.*, 1978).

4.3 Biochemical and cellular effects

4.3.1 Induction of xenobiotic metabolism and oxidative stress

PBBs, like their chlorinated analogues, are ligands for several cellular and nuclear receptors. The earliest description of PCBs as ligands was for the aryl hydrocarbon receptor (AhR) (Bandiera *et al.*, 1982). This binding preceeded the efficacious induction of a broad spectrum of xenobiotic-metabolizing enzymes, most noticeably certain cytochrome P450-dependent monoxygenases (CYPs). PCBs and PBBs increased the activity of CYP2Bs and microsomal epoxide hydrolase (Parkinson *et al.*, 1983), glutathione transferases (Schramm *et al.*, 1985), and UDP-glucuronosyltransferase (Ahotupa & Aitio, 1978).

Of the individual PBB congeners, like PCB congeners with the same substitution pattern, the best ligands for AhR are those isomers and congeners in which halogens are present in the *meta* and *para* positions of biphenyl, but without *ortho* halogens (Robertson *et al.*, 1982, 1983, 1984b). These PBBs are referred to as "coplanar" or "dioxin-like" congeners, typical examples of which are PBB-77, PBB-126, PBB-169. Other halogenated biphenyls, characterized by halogen substitution in the *ortho* and *para* positions of biphenyl (e.g. 2,2′,4,4′,5,5′-hexabromobiphenyl, PBB-153), activate the constitutive androstane receptor (CAR). PBBs in this group induce CYP2B1/2 and as such resemble phenobarbital in their mode of induction of cytochrome P450 (Robertson *et al.*, 1982, 1984b; Parkinson *et al.*, 1983). PBBs with one *ortho* bromine may be mixed-type inducers of CYPs, inducing CYP1A and CYP2B subfamily members (Robertson *et al.*, 1981, 1982).

Although there is great similarity in the modes of induction of cytochrome P450 by PCBs and by PBBs, in terms of potency and efficacy there are a few examples of qualitative differences, and many quantitative differences. 3,4,4′-Tribromobiphenyl (PBB-37) is strictly an inducer of CYP1A in rat liver, while its chloro analogue also induces CYP2B isoforms (Robertson *et al.*, 1982; Parkinson *et al.*, 1983). Andres and co-workers compared the modes of induction and potency of a series of 3,3′,4,4′-tetrahalobiphenyl congeners in which each chlorine atom was sequentially replaced with bromine; the brominated analogues were more potent and more efficacious inducers of cytochrome P450 and much more toxic (Andres *et al.*, 1983).

In a 16-day time-course, Firemaster BP-6 was more efficacious than Aroclor 1254 (both at a dose of 500 mg/kg bw) in repressing hepatic

selenium-dependent glutathione peroxidase activity (Schramm *et al.*, 1985). Given that the average relative molecular mass of Firemaster BP-6 is almost twice that of Aroclor 1254, Firemaster BP-6 had a greater effect at about half the molar dose.

4.3.2 Substrates and inhibitors of xenobiotic metabolism

The metabolic activation of lower halogenated biphenyls to electrophiles and their reaction with cellular substituents, such as proteins and DNA, the production of oxygen-centred radicals, and the biological and toxicological consequences of these reactions, have been explored extensively with individual PCBs and commercial PCB mixtures. However, the same level of attention has not been paid to the PBBs, although it may be assumed that many of the same principles/pathways apply (see *Monograph* on Polychlorinated Biphenyls, Section 4.2 and Section 4.6, in this Volume).

Mills and coworkers investigated the metabolism of PBBs by hepatic microsomes from male rats treated with 3-methylcholanthrene [CYP1A inducer]. The rate of metabolism in decreasing order was PBB-15 (fastest), followed by PBB-37, PBB-77, PBB-56, PBB-70, and PBB-49. The rate of metabolism by hepatic microsomes from male rats treated with phenobarbital [an inducer of CYP2B] was PBB-4 (fastest) followed by PBB-49, PBB-52, PBB-56, PBB-70, and PBB-101. Thus CYP1A preferentially metabolized congeners with adjacent non-halogenated *ortho* and *meta* carbon atoms, while CYP2B preferentially metabolized congeners with adjacent non-halogenated *meta* and *para* carbons on at least one ring (Mills *et al.*, 1985). Also, PBB-169 effectively inhibited the metabolism of PBB-77 at similar concentrations (Mills *et al.*, 1985).

4.3.3 Cell–cell communication and metabolic cooperation

There were three reports that Firemaster BP-6 and individual PBB congeners can inhibit cell–cell communication or metabolic cooperation (Trosko *et al.*, 1981; Tsushimoto *et al.*, 1982; Kavanagh *et al.*, 1987). Firemaster BP-6, and PBB-118, PBB-153, PBB-180, and PBB-194 were reported to exert a dose-related inhibition of metabolic cooperation at concentrations that were relatively non-toxic to cells (Trosko *et al.*, 1981; Tsushimoto *et al.*, 1982). Firemaster BP-6 and PBB-153 displayed dose-dependent inhibition of cell–cell communication (Kavanagh *et al.*, 1987). In contrast, PBB-77, PBB-126, and PBB-169, all three with a dioxin-like activity, were inactive as inhibitors of metabolic cooperation or cell–cell communication at non-cytotoxic concentrations (Tsushimoto *et al.*, 1982; Kavanagh *et al.*, 1987).

4.3.4 Initiation–promotion

Six publications described studies that assessed Firemaster BP-6 and individual PBB congeners (PBB-77, PBB-153, PBB-169, and the combination of PBB-153 and PBB-169) as initiators and promoters of preneoplastic lesions in two-stage models of hepatocarcinogenesis in female Sprague-Dawley rats. All studies found that Firemaster BP-6 and individual PBB congeners were weak initiators, producing a small number of preneoplastic foci when administered alone. In contrast, Firemaster BP-6 and PBB -77, PBB-153, and the combination of PBB-153 and PBB-169 were generally efficacious promoters following an initiation regimen of partial hepatectomy plus NDEA, while PBB-169 alone did not show promoting activity (Jensen *et al.*, 1982, 1983, 1984; Jensen & Sleight, 1986; Rezabek *et al.*, 1987; Dixon *et al.*, 1988).

4.3.5 Other biochemical and cellular effects

In contrast to the PCBs, the PBBs had not yet been investigated for estrogenicity and anti-estrogenicity via estrogen-receptor binding (Gierthy *et al.*, 1997), effects on calcium channels via activation of the ryanodine receptor (Wong *et al.*, 1997), ability to cause insulin release from cells in culture (Fischer *et al.*, 1996), their potency in lowering cellular dopamine levels (Chu *et al.*, 1995), and their ability to activate neutrophils to produce superoxide (Fischer *et al.*, 1998).

4.4 Organ toxicity

In studies of acute toxicity, especially with dioxin-like PBBs, pathological and biochemical changes in the liver are evident in a matter of days. In rats, for example, a single intraperitoneal dose of PBB-77 at 150 µmol/kg resulted in a statistically significant increase in liver weight in 24 hours, and a significant decrease in thymus weight in 4 days (Robertson *et al.*, 1991). Small distinct lipid droplets in hepatocytes were seen histopathologically as early as day 2, while a loss of cortical lymphocytes of the thymus was seen at day 4.

In a 30-day study, mice and rats were given either Firemaster FF-1 or an equal molar equivalent of PBB-153 (Gupta *et al.*, 1981). After 15 days, livers were enlarged due to hepatocyte swelling, fatty infiltration, and proliferation of the endoplasmic reticulum, in animals treated with 3 or 30 mg/kg, and these hepatocellular alterations persisted to 120 days at the highest dose. Firemaster FF-1 was more toxic than PBB-153 (Gupta *et al.*, 1981).

In a long-term study, rats and mice were given Firemaster FF-1 or BP-6 for 6 months (Gupta *et al.*, 1983b; NTP, 1983). Treated rodents showed decreased body-weight gain (despite no change in feed consumption), increased liver weight, and decreased thymus weight. Microscopic changes in the liver included hepatocellular swelling, disorganization, single-cell necrosis, fatty infiltration, and bile-duct proliferation. Levels of hepatic porphyrin were markedly increased, while serum levels of T4 (thyroxine) and T3 (triiodothyronine) were decreased (Gupta *et al.*, 1983b; NTP, 1983). After the 6 months of dosing, the animals were observed for an additional 23 or 24 months. Treated rats showed significantly higher incidence of atypical hepatocellular foci, neoplastic nodules, hepatocellular carcinoma, and cholangiocarcinoma (see Section 3).

Mild microscopic changes in the thyroid gland were also observed in the NTP study (NTP, 1983). Kasza and colleagues carried out a more detailed examination of the effects of PBBs in the rat thyroid. On microscopic (light and electron) examination after short-term dietary exposure, they found ultrastructural lesions consistent with diminished synthesis and secretion of thyroxine (Kasza *et al.*, 1978).

In a subsequent NTP study (NTP, 1993), the effects of exposure to Firemaster FF-1 were investigated in rats and mice exposed as adults, exposed only perinatally (dietary exposure of dams before breeding and throughout gestation and lactation), or exposed both perinatally and as adults. The adult-only exposures demonstrated that the major organ affected by toxicity associated with PBBs was the liver. At 9 months, rats had decreased body weight, hepatomegaly, non-neoplastic histopathological changes, mild anaemia, increased serum cholesterol, and decreased serum triglycerides (males only) (NTP, 1993).

Immunocompetence after exposure to PBBs has been investigated in rodents and birds (Vos & Van Genderen, 1973; Luster *et al.*, 1978), in cattle (Jackson & Halbert, 1974; Kateley & Bazzell, 1978), in swine (Howard *et al.*, 1980), and in humans (Bekesi *et al.*, 1979b, 1987). Exposure of rats to dioxin-like PBBs resulted in rapid loss of cortical thymocytes (Robertson *et al.*, 1991), as described above. In rats exposed to PBBs, the ability to mount an antibody response to an

antigen was impaired. Both cell-mediated and humoral immunity were affected in rats and mice (Vos & Van Genderen, 1973; Luster *et al.*, 1978). Farm cattle given fodder contaminated with PBBs developed a range of symptoms, including atrophic thymus, abnormal lymph nodes, and prolonged infections (Jackson & Halbert, 1974). In contrast, Kateley & Bazzell (1978) did not find evidence of immune system impairment in cattle exposed environmentally, or exposed accidentally to PBBs at much lower levels. In sows fed Firemaster BP-6 at a dose of 100 or 200 ppm during the second half of lactation, the lymphocyte mitogenic response was significantly reduced in piglets tested at age 4 weeks (Howard *et al.*, 1980). In Michigan-farm residents who had consumed food contaminated with PBBs, immune-function abnormalities in vitro were evident in 20–25% (Bekesi *et al.*, 1987) and 35–40% (Bekesi *et al.*, 1979b) of the residents examined.

Endocrine disruption

Several investigations have reported PBB-related effects in individuals exposed during the Michigan poisoning episode of the 1970s (see Section 1.4.4). Dietary exposure to PBBs was associated with an elevated occurrence of self-reported abnormal Pap tests in women; occurrence was lower in exposed women who had breastfed for more than 12 months (Jamieson *et al.*, 2011). Maternal exposure to PBBs was also associated with increased likelihood of a male birth (Terrell *et al.*, 2009) and with increased infant birth weights (Sweeney & Symanski, 2007).

Perinatal exposure of rats to PBBs diminished the effect of exogenously administered estradiol on uterine weight and uterine RNA content. PBBs increased the hepatic microsomal metabolism of estradiol, estrone, and ethynylestradiol in vitro (McCormack *et al.*, 1979; Bonhaus *et al.*, 1981).

4.5 Mechanistic considerations

PBBs are highly lipophilic, and bioconcentrate and bioaccumulate. In mammals, they are transferred through the placenta and in breast milk (McCormack *et al.*, 1981; Kimbrough, 1985; Jacobson *et al.*, 1989). PBBs are efficacious inducers of hepatic metabolism, accelerating the turnover (half-lives) of endogenous and exogenous compounds. An imbalance in metabolizing enzymes may lead to increased oxidative stress through at least three mechanisms, which have been observed with PCBs. Firstly, it has been demonstrated that the persistent induction of CYPs, in the absence of substrate, may lead to the production of reactive oxygen species (Schlezinger *et al.*, 1999, 2000). Secondly, an increase in or induction of certain metabolizing enzymes, especially CYPs and epoxide hydrolase, may steer the metabolism of endogenous and exogenous compounds towards more redox-reactive intermediates, estradiol, PCBs, etc., and increase redox cycling (CYP reductase, DT-diaphorase) (Twaroski *et al.*, 2001). Lastly, a reduction in antioxidants and antioxidant enzymes, such as selenium and selenium-dependent glutathione peroxidase, may cause an increase in oxidative stress through the lowering of antioxidant defenses (Schramm *et al.*, 1985; Twaroski *et al.*, 2001; Lai *et al.*, 2010, 2011).

PBBs display a variety of adverse effects, including immune-system suppression (Bekesi *et al.*, 1979b, 1987), disruption of normal hormone function (McCormack *et al.*, 1979; Bonhaus *et al.*, 1981) and disruption of cell–cell communication. The liver and the immune system are early targets of PBB toxicity. PBBs are weak initiators of rodent two-stage hepatocarcinogenesis and are efficacious promoters in this model system. PBBs produce lesions in the liver and in a variety of other tissues and organs. Other acute adverse biochemical and toxic effects of PBBs are no doubt mediated by the interactions of various PBBs with other sites and cellular receptors.

Much less research has been conducted on PBBs than on PCBs. Commercial PBB mixtures are associated with equivalent or greater toxicity than their chlorinated analogues (Matthews *et al.*, 1978; Andres *et al.*, 1983). It is likely that the congeneric PBBs exhibit their toxicity and disease potential via many of the same pathways as their chlorinated counterparts.

5. Summary of Data Reported

5.1 Exposure data

Polybrominated biphenyls (PBBs) are a class of aromatic compounds consisting of 209 congeners, in which 1–10 bromine atoms are attached to a biphenyl nucleus. The current nomenclature arranges the 209 congeners by increasing numbers of bromine atoms from 1 to 209. PBBs are not known to occur naturally. PBBs are chemically comparable to the polychlorinated biphenyls (PCBs), although the bromine atom is larger than the chlorine atom, and the carbon–bromine bond is weaker than that between carbon and chlorine. PBBs are characterized by low volatility, which decreases with increasing number of substituted bromine, and low solubility in water; they are chemically stable and persistent in the human body, although to a lesser extent than PCBs. Highly brominated PBB congeners tend to debrominate to less brominated congeners.

The analytical methods for detection of PBBs are similar to those for PCBs, but highly sensitive methods are required at low concentrations.

PBBs were produced primarily as flame retardants, as hexa-, octa- and decabromobiphenyls, with bromine content of up to 85% by weight. PBBs were also added to plastics as flakes (up to 10%), and not chemically incorporated into the polymers. Other uses were in coatings and lacquers, and in polyurethane foam.

PBBs have been detected primarily near the sites of production and use; however, detection in biota of remote areas shows that PBBs should be considered as global environmental pollutants. One major episode of human food contamination occurred in Michigan, USA, in which animal feed supplement was contaminated with a commercial PBB mixture. The highest exposure occurred from consuming dairy products from those farms that had received the contaminated feed. As a result of this accident in 1973–1974, PBB production soon ceased in the USA; by 2000, all known production had ceased globally. Workers involved in production were exposed to PBBs through inhalation or dermal contact. Some workers continue to be exposed today through e-waste dismantling and recycling.

Mixed polybromochlorobiphenyls (PXBs) are a class of aromatic compounds with a mixed content of chlorine and bromine atoms attached to the biphenyl nucleus. PXBs have been observed as minor contaminants in some commercial PCB or PBB mixtures, and maybe formed upon disposal of these products at high temperature. PXBs have been detected in environmental and biological samples.

5.2 Human carcinogenicity data

Human data on the carcinogenicity of PBBs were available primarily from follow-up of residents exposed to contaminated food following an industrial accident in Michigan, USA. In a nested case–control analysis, positive findings were observed for lymphoma and cancers of the digestive system combined (including liver, stomach, oesophagus, and pancreas). The cohort was unique, but small, and the risk estimates are imprecise.

5.3 Animal carcinogenicity data

PBBs have been evaluated using a variety of study designs in rats, mice and hamsters, ranging in duration from several months up to 2 years.

These include complete studies of carcinogenicity, studies of carcinogenicity involving transplacental and perinatal exposure, studies assessing promoting activity, using tumours or preneoplastic lesions as an end-point, a study of co-carcinogenicity, and a study of modification of iron metabolism.

Firemaster FF-1, a commercial mixture of PBBs, was tested for carcinogenicity in two studies by gavage or in the diet in male and female mice: FF-1 caused a significant increase in the incidence of hepatocellular carcinoma. In another study of carcinogenicity incorporating adult-only, perinatal-only, and adult-plus-perinatal exposures, Firemaster FF-1 caused significantly increased incidences of hepatocellular adenoma and carcinoma, and hepatocellular adenoma and carcinoma combined. There was also a positive trend for thyroid follicular-cell adenoma in male mice.

Firemaster FF-1 was tested for carcinogenicity in two oral gavage studies in male and female rats: FF-1 caused significantly increased incidences of hepatic neoplastic nodules, hepatocellular carcinoma and (rare) cholangiocarcinoma in male and female rats, and myelomonocytic leukaemia in male rats. In another study of carcinogenicity incorporating adult-only, perinatal-only, and adult-plus-perinatal exposures, Firemaster FF-1 exposure caused significantly increased incidences of hepatocellular adenoma and carcinoma, hepatocellular adenoma and carcinoma combined, and mononuclear cell leukaemia in male and female rats.

In Syrian golden hamsters, Firemaster BP-6 in the diet promoted the development of *N*-nitrosodiethylamine-initiated benign nasal papillomas in one study. Firemaster BP-6 did not promote 7,12-dimethylbenz[*a*]anthracene-initiated skin tumours in one study in mice.

PBB-153 had promoting activity in two studies of *N*-nitrosodiethylamine-induced rat liver carcinogenesis with hepatic nodules and altered hepatic foci as the end-points, but did not have promoting activity in one study of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced mouse skin carcinogenesis.

PBB-169 had promoting activity in one study of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced mouse skin carcinogenesis, but did not have promoting activity in one study of *N*-nitrosodiethylamine-induced rat liver carcinogenesis, although it enhanced the liver tumour promoting activity when administered together with PBB-153.

5.4 Mechanistic and other relevant data

PBBs are highly lipophilic compounds that biocncentrate and bioaccumulate in fatty tissues. PBBs are efficacious inducers of hepatic metabolism, accelerating the turnover (reducing the half-lives) of both endogenous and exogenous compounds. PBBs display a variety of adverse effects including suppression of the immune system and disruption of normal hormone function. PBBs are weak initiators of two-stage hepatocarcinogenesis in rodents, but they are efficacious promoters in these model systems. When administered to rodents by themselves and for longer periods of time, PBBs are carcinogens that produce tumours in the liver and in a variety of other tissues and organs.

While there is an extensive body of literature to assess the carcinogenicity of PCBs (see the *Monograph* on Polychlorinated Biphenyls in this Volume), their brominated analogues have received much less attention and study. Firemaster, a commercial mixture of PBBs, causes aryl hydrocarbon receptor-related toxicity equivalent to or greater than that of their chlorinated analogues. PBBs likely will exhibit their toxicity and disease potential via many of the same pathways as their chlorinated counterparts.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of polybrominated biphenyls.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of Firemaster FF-1.

There is *limited evidence* in experimental animals for the carcinogenicity of polybrominated biphenyl-153.

There is *inadequate evidence* in experimental animals for the carcinogenicity of polybrominated biphenyl-169 and Firemaster BP-6.

6.3 Overall evaluation

Polybrominated biphenyls are *probably carcinogenic to humans (Group 2A)* on the basis of mechanistic similarities to polychlorinated biphenyls.

Rationale for the mechanistic upgrade of polybrominated biphenyls to Group 2A:

- Polybrominated biphenyls share several chemical and physical characteristics with their chlorinated analogues.
- Polybrominated biphenyls are effectively absorbed and distributed, cross the placenta and are detected in milk.
- Polybrominated biphenyls have estimated long half-lives in animal tissues, serum and fat.
- Polybrominated biphenyl congeners are potent and efficacious inducers of xenobiotic-metabolizing enzymes.
- Individual polybrominated biphenyl congeners inhibit cell-to-cell communication or metabolic cooperation.
- Individual congeners PBB-77, PBB-153, PBB-169 are weak initiators and efficacious promoters of two-stage hepatocarcinogenesis.
- Individual polybrominated biphenyls, as for their chlorinated analogues, are ligands for several cellular and nuclear receptors.
- In studies of acute toxicity, pathological and biochemical changes in the liver and thymus are evident in a matter of days.
- In long-term studies, polybrominated biphenyls induce microscopic changes in rodent liver, described as hepatocellular swelling, disorganization, single cell necrosis, fatty infiltration and bile duct proliferation, and mild microscopic changes in thyroid glands.
- Reduced immunocompetence after polybrominated biphenyl exposure was found in rodents, birds, cattle, swine and humans.
- Perinatal exposure of rats to polybrominated biphenyls diminished the effect of exogenously administered estradiol on uterine weight and uterine RNA content. Polybrominated biphenyls increased the hepatic microsomal metabolism of estradiol, estrone and ethynylestradiol in vitro.
- Polybrominated biphenyl exposure in women was also associated with increased odds of a male birth.

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LIST OF ABBREVIATIONS

ABS	acrylonitrile-butadiene-styrene
AMAP	Arctic Monitoring and Assessment Programme
ANZECC	Australian and New Zealand Environment and Conservation Council
ARNT	aryl hydrocarbon receptor nuclear translocator
BHC	benzene hexachloride
BMI	body mass index
BOS	basic oxygen steelmaking
BrdU	bromodeoxyuridine
bw	body weight
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
DEN	diethylnitrosamine
DHEA	dehydroepiandrosterone
DIPN	*N*-nitrosodiisopropanolamine
DLBCL	diffuse large B-cell lymphoma
DL-PCB	dioxin-like PCBs
DMBA	7,12-dimethylbenz[*a*]anthracene
ECNI	electron-capture negative ionization
EBV	Epstein–Barr virus
EBV-EA	Epstein–Barr virus early antigen
EFSA	European Food Safety Authority
EHEN	*N*-ethyl-*N*-hydroxyethylnitrosamine
EPA	Environmental Protection Agency
EROD	ethoxyresorufin *O*-deethylase
e-waste	electronic waste
GC-MS	gas chromatography–mass spectrometry
GGT	gamma-glutamyl transferase
GJIC	gap-junctional intercellular communication
GPC	gel permeation chromatography
GSH	glutathione
GST	glutathione *S*-transferase
OH-PCBs	hydroxylated PCBs
HR	hazard ratio
HRGC	high-resolution gas chromatography
HRMS	high-resolution mass spectrometry

IRR	incidence rate ratio
JEM	job-exposure matrix
LLE	liquid-liquid extraction
MDAB	3'-methyl-4-dimethylaminoazobenzene
MNNG	*N*-methyl-*N*'-nitro-*N*-nitrosoguanidine
NDEA	*N*-nitrosodiethylamine
NDL-PCBs	non-dioxin-like PCBs
NDMA	*N*-nitrosodimethylamine
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NIOSH	National Institute for Occupational Safety and Health
NK	natural killer
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NTP	National Toxicology Program
PAH	polycyclic aromatic hydrocarbons
PBB	polybrominated biphenyl
PBDE	polybrominated diphenyl ether
PBMC	peripheral blood mononuclear cells
PBN	polybrominated naphthalene
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PeCDF	2,3,4,7,8-pentachlorodibenzofuran
PEL	permissible exposure limit
PLE	pressurized liquid extraction
PXB	polybromochlorobiphenyl
PXR	pregnane-X receptor
RR	rate ratio
SIR	standardized incidence ratio
siRNA	small interfering RNA
SMR	standardized mortality ratio
SPE	solid-phase extraction
SHBG	steroid hormone-binding globulin
T3	triiodothyronine
T4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*para*-dioxin
TWA	time-weighted average
TEF	toxic equivalence factor
TEQ	toxic equivalency
TNF	tumour necrosis factor
TSH	thyroid-stimulating hormone
TTR	transthyretin; thyroid hormone transport protein; thyroxine-binding protein
UDPGT	uridine diphosphoglucuronyl transferase

IARC MONOGRAPHS

This volume of the *IARC Monographs* provides evaluations of the carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls.

Polychlorinated biphenyls are a class of aromatic compounds comprising 209 congeners, each containing 1 to 10 chlorine atoms attached to a biphenyl nucleus. Technical products, which were manufactured to obtain a certain degree of chlorination, are mixtures of numerous congeners. These products were widely used as dielectric fluid in capacitors and transformers, and to a lesser extent in building materials. Although their production and use has been banned in most countries, these compounds are ubiquitous environmental pollutants, including in polar regions and the deep ocean, because they are persistent and bioaccumulate. Worldwide monitoring programmes have shown that polychlorinated biphenyls are present in most samples of human milk.

An *IARC Monographs* Working Group reviewed epidemiological evidence, animal bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans of polychlorinated biphenyls, of the subclass of dioxin-like polychlorinated biphenyls, and of polybrominated biphenyls.