NR 2012;46(1)

The Nordic Expert Group for Criteria Documentation
of Health Risks from Chemicals

146. Polychlorinated biphenyls (PCBs)

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ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE

ISBN 978-91-85971-35-0 ISSN 0346-7821

UNIVERSITY OF GOTHENBURG

ARBETSMILJÖ VERKET

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by Occupational and Environmental Medicine at Sahlgrenska Academy, University of Gothenburg. The series publishes scientific original work, review articles, criteria documents and dissertations. All articles are peer-reviewed.

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Arbete och Hälsa, University of Gothenburg
SE 405 30 Gothenburg, Sweden

ISBN 978-91-85971-35-0
ISSN 0346–7821
http://www.amm.se/aoh

Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. No numerical values for occupational exposure limits are proposed. Whereas NEG adopts the documents by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document on polychlorinated biphenyls (PCBs) was done by M Ph Birgitta Lindell, Swedish Work Environment Authority, Stockholm. The draft versions were discussed within NEG and the final version was accepted by the present NEG experts on May 24, 2011. Editorial work and technical editing were performed by the NEG secretariat. The following present and former experts participated in the elaboration of the document:

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This work was financially supported by the Swedish Work Environment Authority and the Norwegian Ministry of Labour.

All criteria documents produced by Nordic Expert Group may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

Contents

Abbreviations and acronyms

ADHD	attention deficit hyperactivity disorder
Ah	aryl hydrocarbon
ALAT	alanine aminotransferase
ALS	amyotrophic lateral sclerosis
ASAT	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CALUX	chemical-activated luciferase gene expression
CAS	Chemical Abstracts Service
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CYP	cytochrome P450
DDE	*p,p′*-dichlorodiphenyldichloroethylene
DDT	*p,p′*-dichlorodiphenyltrichloroethane
DFI	DNA fraction index
DPOAE	distortion product otoacoustic emission
DSA	delayed spatial alternation
EC_{50}	half maximal effective concentration: a described effect is found in 50 % of the exposed animals or the effect is 50 % of the control value
ECD	electron capture detection
EFSA	European Food Safety Authority
EI	electron impact
EPA	Environmental Protection Agency
EROD	ethoxyresorufin-*O*-deethylase
EU	European Union
GABA	γ-aminobutyric acid
GC	gas chromatography
GLUT	glucose transporter protein
GSCL	Giessen Subjective Complaints List
GST	glutathione-*S*-transferase
HLA	human leukocyte antigen
IARC	International Agency for Research on Cancer
IC_{50}	50 % inhibition concentration
Ig	immunoglobulin
IL	interleukin
IPCS	International Programme on Chemical Safety
IQ	intelligence quotient
IRS	insulin receptor substrate
IUPAC	International Union of Pure and Applied Chemistry
LD_{50}	lethal dose for 50 % of the exposed animals at single administration
LOAEL	lowest observed adverse effect level
MFO	mixed-function oxidase
MS	mass spectrometry/mass spectrometric detection
NBAS	neonatal behavioural assessment scale

NCI	negative chemical ionisation
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin's lymphoma
NMDA	*N*-methyl-*D*-aspartate
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
POP	persistent organic pollutant
RCQ	redox-cycling quinone
ROS	reactive oxygen species
RR	risk ratio
SIR	standard incidence ratio
SMR	standard mortality ratio
T_3	triiodothyronine
T_4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEF	toxic equivalency factor
TEQ	toxic equivalent
TNFα	tumour necrosis factor alpha
TSH	thyroid-stimulating hormone
TWA	time-weighted average
UDP-GT	uridine diphospho-glucuronosyl transferase
US	United States
WHO	World Health Organization
WISC	Wechsler Intelligence Scales for Children

1. Introduction

Polychlorinated biphenyls (PCBs) are a class of 209 congeners, in which 1–10 chlorine atoms are attached to biphenyl in different combinations. The PCBs have been commercially produced as complex mixtures since 1929. Because of their chemical and physical stability and electrical insulating properties, they have had a variety of uses in industry. However, due to their harmful effect on the environment, the production and use of PCBs is banned or restricted worldwide. Therefore, PCBs are nowadays mainly regarded as ubiquitous environmental pollutants, but they can still occur in work environments, especially when renovating and demolishing buildings and in recycling and waste management.

This document was initiated with the intention to focus on possible effects on human health from occupational exposure of PCBs today, but such data are scarce, although new data have been published on cohorts exposed long ago. Since there are indications that effects may occur in the general population at PCB body burdens in the range of those expected from daily intake, data on the general population were considered relevant and were included in the document. Yet, it should be noted that the congener pattern at exposure from food differs from that at occupational exposure. Selected data on toxic effects in experimental animals are also reviewed. For a number of toxicological endpoints, the no-effect levels in rodents and monkeys are high (in the low mg/kg body weight (bw)/day range for technical PCB mixtures), and these endpoints are described very briefly or not at all in this document.

PCB levels expressed in the original publications as ppb or µg/kg (ng/g) wet weight in serum, plasma or whole blood are stated as µg/l throughout this document, whereas lipid-adjusted values are given as ng/g lipid.

As a basis for this document, we have used previously published reviews, mainly those produced by the World Health Organization/International Programme on Chemical Safety (WHO/IPCS), 2003 (188), the Agency for Toxic Substances and Disease Registry (ATSDR), 2000 (19) and the European Food Safety Authority (EFSA), 2005 (98).

2. Substance identification

PCBs are aromatic compounds, which do not occur naturally. In the PCB molecule, 1–10 chlorine atoms are attached to biphenyl (Figure 1). The general chemical formula is $C_{12}H_{(10-n)}Cl_n$, where n is the number of chlorine atoms. Depending on position and number of chlorine atoms, there are theoretically 209 individual PCB compounds (congeners). These PCB compounds can be categorised by degree of chlorination in ten homologue groups (Table 1). PCBs of a given homologue with different substitution patterns are called isomers.

The conventional *numbering* of substituent positions is shown in Figure 1. In 1980, Ballschmiter and Zell developed a numbering system that gives a specific BZ number to each PCB congener. The congeners were numbered from PCB 1 to PCB 209 in ascending order based on the number of chlorine substitutions within

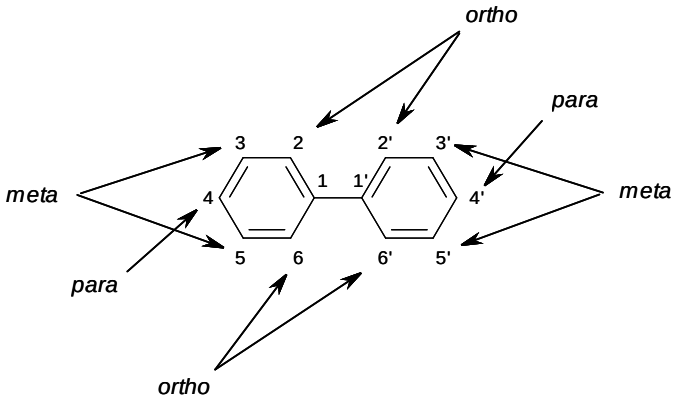

Figure 1. Biphenyl molecule according to the IUPAC numbering system. In PCBs, some or all of the hydrogens attached to carbon atoms numbered 2–6 and 2′–6′ are substituted with chlorines.

each homologue. An unprimed number was considered lower than the same number when primed (Figure 1) (25). Slight changes in the original BZ congener numbering system have later been recommended. These changes included a re-numbering of the BZ numbers 107, 108, 109 to 109, 107, 108 and of BZ numbers 199, 200, 201 to 200, 201 and 199, respectively. However, in general, authors have not adopted the revised numbering of congeners 107–109. Thus, the numbering system commonly used is that published by Ballschmiter *et al* (1992), where only the original BZ numbers 199–201 are changed (188, 270). A *nomenclature* for PCB congeners based on the International Union of Pure and Applied Chemistry (IUPAC) is shown in Table 2. The relation between PCB congener numbers and the Chemical Abstracts Service (CAS) numbers is shown in Table 3.

In the biphenyl molecule, the two benzene rings can rotate around the 1,1′-bond (Figure 1). The two extreme configurations are the planar, in which the two benzene rings are in the same plane, and the non-planar in which the benzene rings are at a 90° angle to each other. The probability of attaining a planar configuration is largely determined by the number of substitutions in the *ortho*-positions (2, 2′, 6, 6′). The replacement of hydrogen atoms in the *ortho*-positions with larger chlorine atoms

Table 1. The PCB homologue groups (103).

Homologue group	CAS No. of group	No. of isomers	Congener No.	Molecular weight	Chlorine (% w/w)
Monochlorobiphenyl	27323-18-8	3	PCB 1 – PCB 3	188.7	19
Dichlorobiphenyl	25512-42-9	12	PCB 4 – PCB 15	223.1	32
Trichlorobiphenyl	25323-68-6	24	PCB 16 – PCB 39	257.6	41
Tetrachlorobiphenyl	26914-33-0	42	PCB 40 – PCB 81	292.0	49
Pentachlorobiphenyl	25429-29-2	46	PCB 82 – PCB 127	326.4	54
Hexachlorobiphenyl	26601-64-9	42	PCB 128 – PCB 169	360.9	59
Heptachlorobiphenyl	28655-71-2	24	PCB 170 – PCB 193	395.3	63
Octachlorobiphenyl	55722-26-4	12	PCB 194 – PCB 205	429.8	66
Nonachlorobiphenyl	53742-07-7	3	PCB 206 – PCB 208	464.2	69
Decachlorobiphenyl	2051-24-3	1	PCB 209	498.7	71
All PCBs	1336-36-3	209	PCB 1 – PCB 209	–	–

CAS: Chemical Abstracts Service, w: weight.

Table 2. Nomenclature conversion table (PCB congener numbers in bold) [a, b] (188).

Chlorine position on each ring	None	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	**0**	**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**[c]	**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] For a number of PCB congeners, the indicated (truncated) structural names are not according to strict IUPAC rules (primed and unprimed numbers are interchanged). A comprehensive survey of the PCB nomenclature, including IUPAC names, is given in Mills *et al,* 2007 (270).

[b] Revised PCB numbering system (includes also the revised numbering of congeners 107-109).

[c] Example: The IUPAC name for PCB 100 is 2,2′,4,4′,6-pentachlorobiphenyl.

☐ = dioxin-like congeners (also included in the WHO TEF and TEQ concept, for details see page 5).

IUPAC: International Union of Pure and Applied Chemistry.

Table 3. PCB congener numbers [a] (in bold) versus CAS numbers. Adapted from US EPA (397).

1	2051-60-7	**26**	38444-81-4	**51**	68194-04-7	**76**	70362-48-0	**101**	37680-73-2	**126**	57465-28-8	**151**	52663-63-5	**176**	52663-65-7	**201**	40186-71-8
2	2051-61-8	**27**	38444-76-7	**52**	35693-99-3	**77**	32598-13-3	**102**	68194-06-9	**127**	39635-33-1	**152**	68194-09-2	**177**	52663-70-4	**202**	2136-99-4
3	2051-62-9	**28**	7012-37-5	**53**	41464-41-9	**78**	70362-49-1	**103**	60145-21-3	**128**	38380-07-3	**153**	35065-27-1	**178**	52663-67-9	**203**	52663-76-0
4	13029-08-8	**29**	15862-07-4	**54**	15968-05-5	**79**	41464-48-6	**104**	56558-16-8	**129**	55215-18-4	**154**	60145-22-4	**179**	52663-64-6	**204**	74472-52-9
5	16605-91-7	**30**	35693-92-6	**55**	74338-24-2	**80**	33284-52-5	**105**	32598-14-4	**130**	52663-66-8	**155**	33979-03-2	**180**	35065-29-3	**205**	74472-53-0
6	25569-80-6	**31**	16606-02-3	**56**	41464-43-1	**81**	70362-50-4	**106**	70424-69-0	**131**	61798-70-7	**156**	38380-08-4	**181**	74472-47-2	**206**	40186-72-9
7	33284-50-3	**32**	38444-77-8	**57**	70424-67-8	**82**	52663-62-4	**107**	70424-68-9	**132**	38380-05-1	**157**	69782-90-7	**182**	60145-23-5	**207**	52663-79-3
8	34883-43-7	**33**	38444-86-9	**58**	41464-49-7	**83**	60145-20-2	**108**	70362-41-3	**133**	35694-04-3	**158**	74472-42-7	**183**	52663-69-1	**208**	52663-77-1
9	34883-39-1	**34**	37680-68-5	**59**	74472-33-6	**84**	52663-60-2	**109**	74472-35-8	**134**	52704-70-8	**159**	39635-35-3	**184**	74472-48-3	**209**	2051-24-3
10	33146-45-1	**35**	37680-69-6	**60**	33025-41-1	**85**	65510-45-4	**110**	38380-03-9	**135**	52744-13-5	**160**	41411-62-5	**185**	52712-05-7		
11	2050-67-1	**36**	38444-87-0	**61**	33284-53-6	**86**	55312-69-1	**111**	39635-32-0	**136**	38411-22-2	**161**	74472-43-8	**186**	74472-49-4		
12	2974-92-7	**37**	38444-90-5	**62**	54230-22-7	**87**	38380-02-8	**112**	74472-36-9	**137**	35694-06-5	**162**	39635-34-2	**187**	52663-68-0		
13	2974-90-5	**38**	53555-66-1	**63**	74472-34-7	**88**	55215-17-3	**113**	68194-10-5	**138**	35065-28-2	**163**	74472-44-9	**188**	74487-85-7		
14	34883-41-5	**39**	38444-88-1	**64**	52663-58-8	**89**	73575-57-2	**114**	74472-37-0	**139**	56030-56-9	**164**	74472-45-0	**189**	39635-31-9		
15	2050-68-2	**40**	38444-93-8	**65**	33284-54-7	**90**	68194-07-0	**115**	74472-38-1	**140**	59291-64-4	**165**	74472-46-1	**190**	41411-64-7		
16	38444-78-9	**41**	52663-59-9	**66**	32598-10-0	**91**	68194-05-8	**116**	18259-05-7	**141**	52712-04-6	**166**	41411-63-6	**191**	74472-50-7		
17	37680-66-3	**42**	36559-22-5	**67**	73575-53-8	**92**	52663-61-3	**117**	68194-11-6	**142**	41411-61-4	**167**	52663-72-6	**192**	74472-51-8		
18	37680-65-2	**43**	70362-46-8	**68**	73575-52-7	**93**	73575-56-1	**118**	31508-00-6	**143**	68194-15-0	**168**	59291-65-5	**193**	69782-91-8		
19	38444-73-4	**44**	41464-39-5	**69**	60233-24-1	**94**	73575-55-0	**119**	56558-17-9	**144**	68194-14-9	**169**	32774-16-6	**194**	35694-08-7		
20	38444-84-7	**45**	70362-45-7	**70**	32598-11-1	**95**	38379-99-6	**120**	68194-12-7	**145**	74472-40-5	**170**	35065-30-6	**195**	52663-78-2		
21	55702-46-0	**46**	41464-47-5	**71**	41464-46-4	**96**	73575-54-9	**121**	56558-18-0	**146**	51908-16-8	**171**	52663-71-5	**196**	42740-50-1		
22	38444-85-8	**47**	2437-79-8	**72**	41464-42-0	**97**	41464-51-1	**122**	76842-07-4	**147**	68194-13-8	**172**	52663-74-8	**197**	33091-17-7		
23	55720-44-0	**48**	70362-47-9	**73**	74338-23-1	**98**	60233-25-2	**123**	65510-44-3	**148**	74472-41-6	**173**	68194-16-1	**198**	68194-17-2		
24	55702-45-9	**49**	41464-40-8	**74**	32690-93-0	**99**	38380-01-7	**124**	70424-70-3	**149**	38380-04-0	**174**	38411-25-5	**199**	52663-75-9		
25	55712-37-3	**50**	62796-65-0	**75**	32598-12-2	**100**	39485-83-1	**125**	74472-39-2	**150**	68194-08-1	**175**	40186-70-7	**200**	52663-73-7		

[a] The numbering presented in the table is identical to that published by Ballschmiter *et al*, 1992 (270).

□ = dioxin-like congeners (also included in the WHO TEF and TEQ concept, for details see page 5).

CAS: Chemical Abstracts Service, EPA: Environmental Protection Agency, US: United States.

forces the benzene rings to rotate out of the planar configuration. The benzene rings of non-*ortho*-substituted PCBs (n = 20), as well as mono-*ortho*-substituted PCBs (n = 48), may assume a planar configuration and are referred to as planar or coplanar congeners. The benzene rings of other congeners cannot assume a planar or coplanar configuration and are referred to as non-planar or non-coplanar congeners (19, 116, 285, 397).

Among the planar PCBs, 4 non-*ortho* and 8 mono-*ortho* PCBs chlorinated in both *para* and at least two *meta* positions are (nowadays) referred to as dioxin-like PCBs (or aryl hydrocarbon (Ah) receptor agonists) (Table 2) and have been included in the WHO TEF and TEQ concept (166, 271, 402). Each of these 12 PCB congeners is attributed a specific toxic equivalency factor (TEF), which indicates the degree of dioxin-like toxicity compared to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which itself has been assigned a TEF of 1.0 (19, 402) (Table 4). PCBs 126 and 169 are the most toxic congeners in this respect with TEFs of 0.1 and 0.03, respectively. The contribution of a congener to the degree of toxicity also depends on the exposure level. For dioxin-like compounds, this can be expressed as total toxic equivalents (TEQs). The sum of TEQs for a mixture is calculated by multiplying the concentration of each dioxin-like compound (e.g. the 12 PCBs) with its assigned TEF and then adding the resulting TEQ concentrations. For inclusion in the TEF concept, a compound must 1) show a structural relationship to the polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), 2) bind to the Ah receptor, 3) elicit Ah receptor-mediated biochemical and toxic responses and 4) be persistent and accumulate in the food chain (1, 402).

Table 4. PCB-toxic equivalency factors (TEFs) (1, 397, 401, 402).

Congener No.	IUPAC chlorobiphenyl prefix	WHO 1994 Humans	WHO 1997 Humans/ mammals	WHO 2005 Humans/ mammals
Non-ortho substituted				
PCB 77	3,3′,4,4′-Tetra-	0.0005	0.0001	0.0001
PCB 81	3,4,4′,5-Tetra-	–	0.0001	0.0003
PCB 126	3,3′,4,4′,5-Penta-	0.1	0.1	0.1
PCB 169	3,3′,4,4′,5,5′-Hexa-	0.01	0.01	0.03
Mono-ortho substituted				
PCB 105	2,3,3′,4,4′-Penta-	0.0001	0.0001	0.00003
PCB 114	2,3,4,4′,5-Penta-	0.0005	0.0005	0.00003
PCB 118	2,3′,4,4′,5-Penta-	0.0001	0.0001	0.00003
PCB 123	2,3′,4,4′,5′-Penta-	0.0001	0.0001	0.00003
PCB 156	2,3,3′,4,4′,5-Hexa-	0.0005	0.0005	0.00003
PCB 157	2,3,3′,4,4′,5′-Hexa-	0.0005	0.0005	0.00003
PCB 167	2,3′,4,4′,5,5′-Hexa-	0.00001	0.00001	0.00003
PCB 189	2,3,3′,4,4′,5,5′-Hepta-	0.0001	0.0001	0.00003
Di-ortho substituted [a]				
PCB 170	2,2′,3,3′,4,4′,5-Hepta-	0.0001	–	–
PCB 180	2,2′,3,4,4′,5,5′-Hepta-	0.00001	–	–
Reference compound				
TCDD		1.0	1.0	1.0

[a] These PCBs were withdrawn from the WHO TEF concept for dioxin-like compounds at the re-evaluation in 1997.

IUPAC: International Union of Pure and Applied Chemistry, TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, WHO: World Health Organization.

3. Physical and chemical properties

Pure single PCB compounds are mostly colourless or slightly yellowish, often crystalline compounds. Commercial products, however, are liquid mixtures of these compounds with a colour ranging from light yellow to dark colour. They do not crystallise at low temperatures but turn into solid resins (73, 188). Physical and chemical data for some of the most toxic and/or environmentally prevalent PCB congeners and for some PCB mixtures (i.e. Aroclors, trade name used in Unites States (US)) are given in Tables 5–6, respectively.

In general, PCBs are relatively insoluble in water, with the highest solubilities among the *ortho*-chlorinated congeners. Solubility decreases rapidly in the *ortho*-vacant congeners and decreases further with increased chlorination (19, 188). All PCB congeners are lipophilic and dissolve easily in non-polar organic solvents and in biological lipids (188, 419). Furthermore, PCBs are relatively non-volatile (188), although lower chlorinated PCB congeners have a considerably higher vapour pressure than the higher chlorinated ones. Therefore, the composition in air is dominated by the lower chlorinated congeners (98). In consequence, the vapour pressure of more low-chlorinated PCB mixtures is higher than that of highly chlorinated PCB mixtures. Because of the chlorine in the molecule, the density of PCBs is rather high (Table 6).

Many of the congeners are very persistent in both the environment and within biological systems (56, 419). PCBs generally are characterised by chemical and physical inertness. They resist both acids, alkalis and oxidants and are, in practice, fire-resistant because of their high flash-points (187, 188, 419). However, at high temperatures, PCBs are combustible. Combustion by-products include hydrogen chloride and PCDFs. Pyrolysis of technical-grade materials containing PCBs and chlorobenzenes (such as some dielectric fluids) may also produce PCDDs (188).

Conversion factors for different PCB mixtures depend on the degree of chlorination and are between 0.065 (Aroclor 1260) and 0.12 ppb (Aroclor 1221) for 1 $\mu g/m^3$ (419).

4. Occurrence, production and use

PCBs were originally synthesised in 1881 by the German chemists Schmidt and Schulz. PCBs have been industrially manufactured as mixtures for commercial purposes since 1929. The total global PCB production between 1930 and 1993 has been estimated to around 1.3 million tonnes, of which more than 70 % are tri-, tetra- and pentachlorinated congeners (44). About one third of the total amount has ended up in the environment (434). The production decreased in the mid-1970s because the chemicals had become a severe environmental problem (143). However, PCBs are still present in the environment and their entry into it still occurs, especially due to improper disposal practices or leaks in electrical equipment and hydraulic systems still in use. Further, PCB caulk and paint in buildings can cause extensive PCB contamination of the building interiors and surrounding soil (168).

Table 5. Physical and chemical data for some of the most toxic and/or environmentally prevalent PCB congeners (19, 188, 380).

Congener	Molecular formula	Melting point (°C)	Boiling point (°C)	Vapour pressure (10^{-6} kPa at 25°C)	Log K_{ow}	Water solubility (µg/l)
PCB 1 [a]	$C_{12}H_9Cl$	34	274	184	4.5	4 830 (25°C)
PCB 77	$C_{12}H_6Cl_4$	173	360 [b]	0.06	6.0–6.6	175 (25°C)
				2.18		0.6 (25°C)
PCB 81	$C_{12}H_6Cl_4$	-	-	-	-	-
PCB 105	$C_{12}H_5Cl_5$	-	-	0.87	7.0	3.4 (25°C)
PCB 118	$C_{12}H_5Cl_5$	-	-	1.20	7.1	13.4 (20°C)
PCB 126	$C_{12}H_5Cl_5$	-	-	-	-	-
PCB 138	$C_{12}H_4Cl_6$	78.5–80	400 [b]	0.53	6.5–7.4 [b]	15.9 [b]
						1.5 (20°C)
PCB 153	$C_{12}H_4Cl_6$	103–104	-	0.05	6.7	0.9 (25°C)
				0.12	8.3	
				0.46	7.8	
PCB 156	$C_{12}H_4Cl_6$	-	-	0.21	7.6	5.3 (20°C)
PCB 163	$C_{12}H_4Cl_6$	-	-	0.08	7.2	1.2 (25°C)
PCB 169	$C_{12}H_4Cl_6$	201–202	-	0.05	7.4	0.04–12.3 [b]
				0.08		0.5 (25°C)
PCB 180	$C_{12}H_3Cl_7$	109–110	240–280	0.13	6.7–7.2 [b]	0.2 (25°C)
			(2.66 kPa)		8.3	0.3–6.6 [b]
						3.9 (20°C)
PCB 183	$C_{12}H_3Cl_7$	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.

Table 6. Approximate homologue composition and physical properties of some commercial PCB products (73, 103).

	Aroclor						
	1221	1232	1016	1242	1248	1254	1260
Composition (%)							
Biphenyl	11	6	< 0.01	-	-	-	-
Monochlorobiphenyl	51	26	1	1	-	-	-
Dichlorobiphenyl	32	29	20	17	1	-	-
Trichlorobiphenyl	4	24	57	40	23	-	-
Tetrachlorobiphenyl	2	15	21	32	50	16	-
Pentachlorobiphenyl	0.5	0.5	1	10	20	60	12
Hexachlorobiphenyl	-	-	< 0.01	0.5	1	23	46
Heptachlorobiphenyl	-	-	-	-	-	1	36
Octachlorobiphenyl	-	-	-	-	-	-	6
Properties							
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
Water solubility (µg/l at 25°C)	200, 15 000 [a]	1 450 [a]	240, 420	240	52, 54	12	3
Vapour pressure (10^{-6} kPa at 25°C)	893	613	53	53	53	11	5.3
Log K_{ow}	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.
K_{ow}: octanol/water partition coefficient.

A significant part of human exposure to PCB derives from food. Food of animal origin is the main contributor to dietary PCB exposure (98).

PCBs have been manufactured under several trade names of which the most well known are Aroclor (US), Clophen (Germany) and Kanechlor (Japan) (Table 7) (103, 187). Depending on the production conditions, the degree of chlorination of PCB mixtures can be up to 68 %. The homologue composition of the mixtures varies greatly (Table 6) and the concentrations of single isomers within each homologue group also deviate from each other in different products and batches. About 130 of the 209 congeners have been identified in commercial formulations at concentrations above 0.05 %. Generally, technical mixtures of PCBs consist of about 70–100 PCB congeners with mono- and non-*ortho* substituted PCBs as minor or trace constituents. Technical PCB mixtures also contain other dioxin-like compounds such as PCDFs as impurities (98, 162, 187, 252). It has been noticed that the total aryl hydrocarbon TEQs for different batches of the same Aroclor may differ considerably (78).

Due to their low electrical conductivity in connection with high thermal conductivity and thermal resistance, the PCBs have been used as cooling liquids in electrical equipment such as transformers and capacitors. PCBs have also been used as hydraulic oils, in heat-exchange systems and in vacuum pumps. Besides this usage in closed systems, large amounts of PCBs were used for other applications, e.g. inks, dyes, paints, surface coatings, sealants, caulking materials, adhesives, flame retardants, pesticide formulations, plasticisers, cutting and lubricating oils (18, 98, 103, 162, 187, 269). In western countries, PCBs were used in public building construction for various purposes in the 1960s and 1970s, mainly as an additive to caulk, grouts and paints. PCBs were also used as a major constituent of permanent elastic sealants on polysulphide rubber basis and as flame retardant coatings of acoustic ceiling tiles (162). In Sweden, PCBs were extensively used as plasticisers in elastic sealants used in joints between concrete blocks in buildings from 1956 to 1972 (378).

Because of the toxic properties, persistence, and bioaccumulation of PCBs in the environment, PCB production and use is banned or restricted worldwide (44, 64, 187, 188). In the US, the production, use and distribution of PCBs were banned in 1979 except in completely closed systems (129, 398). In the European Union (EU), open applications were banned in 1976 (Dir 76/403/EEC) and in the EU

Table 7. Trade names of PCB products and PCB containing mixtures (187).

Aceclor	Clophen	Hivar	Polychlorobiphenyl
Apirolio	Clorphen	Hydol	Pydraul
Aroclor	Delor	Inclor	Pyralene
Arubren	Diaclor	Inerteen	Pyranol
Asbestol	Dialor	Kanechlor	Pyroclor
Askarel	Disconon	Kennechlor	Saf-T-Kuhl
Bakola 131	Dk	Montar	Santotherm FR
Biclor	Duconol	Nepolin	Santovac
Chlorextol	Dykanol	No-Flomol	Siclonyl
Chlorinaol	EEC-18	PCB	Solvol
Chlorinated Biphenyl	Elemex	PCBs	Sovol
Chlorinated Diphenyl	Eucarel	Phenoclor	Therminol FR
Chlorobiphenyl	Febchlor	Polychlorinated biphenyl	

directive from 1996 (Dir 96/59/EC) it was stated that a complete phase out should be reached before 2010 (108). In Sweden, the use of PCBs was restricted in 1972 and allowed only in closed systems. New equipment containing PCBs was prohibited from 1978, whereas old installations containing PCBs were allowed until 1995 (2, 32). Buildings containing PCB shall be decontaminated by the latest in 2016 (379). No new PCB-containing products have been allowed in Norway since 1980, in Finland since 1985, in Denmark since 1986 and in Iceland since 1988 (2).

5. Measurements and analysis of workplace exposure

The quantification of PCBs in biological samples usually consists of three distinct steps: extraction of PCBs from the sample matrix by solvents, removal of impurities on columns, and quantification by gas chromatography (GC) with a suitable detector (188). Serum is considered a suitable matrix for occupational and environmental exposure estimation. It is homogenous and does not coagulate during freezing. Also plasma is often used as matrix in many laboratories (20).

The extraction of lipophilic PCBs from serum or plasma is mostly done with solvents or solvent mixtures like hexane:dichloromethane (306), hexane:diethyl ether (53), hexane (142) or acetonitrile (431). The solvent extract is often washed with acid or base to remove large quantities of organic co-extractives. This ensures that subsequent commonly used column chromatography procedures are not overloaded by organic material. Adsorbent columns reported for sample purification include silica gel (20, 201, 431), Florisil (88, 201, 306, 363), carbon (130), basic alumina (201), potassium silicate (431) and acid impregnated silica gel columns (431). Also liquid-lipophilic gel partitioning as the lipid extractive step without acid treatment has been reported for blood samples (290, 417). During extraction and sample clean-up, care has to be taken to avoid losses of the lower chlorinated PCB congeners due to their relatively high volatility (98).

At air sampling, samples are taken either from the general workplace air or the breathing zone of workers. Usually, Florisil or XAD-2 adsorbent tubes are used with or without glass fibre filters placed in front of the tube. Using both adsorbent and filter ensures that PCBs in both gas and particulate form are collected (213).

Surface sampling of PCBs can be carried out by the wet-wipe procedure at which an area is wiped with a cotton gauze pad dampened with hexane (187).

Recovery of various PCB mixtures (16–54 % chlorinated) was 94–100 % in dust samples collected on glass fibre filters and solid sorbent sampling (Florisil, OVS sampler, XAD-2) (278, 286).

Modern techniques for identification and quantification are mainly based on GC with electron capture detection (ECD) or mass spectrometric detection (MS). Capillary or high-resolution GC has made it possible to achieve lower detection limits and better separation of individual PCB congeners for quantification, and today high-resolution GC-ECD is the analytical method of choice (19, 51, 88, 98, 142, 188, 255, 419). For the non-*ortho* PCB congeners, and preferably also for the mono-*ortho*-substituted PCBs, MS must be used (419). MS has also been recommended when multiple individual congener measurements are required,

although recently GC-μECD has been proposed suitable for mass screening (45, 188).

A detection limit of 1 ng/l in human plasma was reported with GC-μECD (45). GC-MS in electron impact (EI) mode has been used in some studies to identify individual congeners (130, 201, 290, 291, 431), but has been reported to be less sensitive than GC-ECD (51, 363). However, using GC-MS with negative chemical ionisation (NCI) can improve the sensitivity. The detection limits for 24 individual congeners varied from 10 to 80 ng/l in serum for GC-MS-NCI (212).

In air samples, PCBs are often determined by GC-ECD, but also GC-MS-EI can be used. The detection limits vary from low ng/m^3 to μg/m^3 for GC-ECD (19). With GC-MS-EI, detection limits less than 1 pg/m^3 have been reported (79).

6. Exposure data

The levels of PCBs in human food, the exposure in the general population, accidental exposures and occupational exposures were discussed in depth by IPCS, 1993 (187). The present document focuses on more recent data on occupational exposure, but contains also some data on background exposure in the general population. Food of animal origin is a main source of PCB exposure and exposure is mainly to the high-chlorinated PCB congeners that accumulate in the food chain. Some exposure to more low-chlorinated PCBs may occur from air, e.g. in contaminated buildings (19, 125, 349). In occupational settings, inhalation is a major exposure route to PCBs (18, 19, 188), at least if respirators are not used, but dermal exposure as well as ingestion of PCBs have been demonstrated and may be of importance (252, 299). Occupational exposure may be to both high- and low-chlorinated PCBs, but the latter constitute a minor part of the PCB load in blood at current low-level exposure (98, 169, 253, 354, 423).

Usually, the sum of some indicator congeners is used to describe PCB levels. The six individual PCB congeners 28, 52, 101, 138, 153 and 180 are often used as indicators to assess environmental exposure. Sometimes, a seventh congener, PCB 118, is included into the group of indicator PCBs (98, 423).

6.1 Environmental exposure

6.1.1 General

Food ingestion is the major route of PCB exposure in the general population (18, 98). The congener pattern for different food products varies. Vegetables account for a major part of the intake of lower chlorinated congeners, whereas fatty foods such as fish, dairy products and meat play a greater role for exposure to higher chlorinated PCBs (19). The relative contribution from different food items varies a great deal between countries. In Finland, about 85 % of the total PCB load of occupationally non-exposed persons originates from fish consumption (409), whereas in Sweden it is estimated that 57 % of the total PCB intake originates from fish and fish products (84). In Sweden, the daily intake of non-dioxin-like PCBs (sum of 23 congeners) was calculated based on a national dietary survey

1997–98 and analytical data from food samples. The calculated median daily intake (1 207 persons) by men and women of different age groups (17–75 years) was found to be in the range of 6.2–9.6 ng/kg bw and 5.5–12 ng/kg bw, respectively (98). However, there are subpopulations, e.g. fishermen, with higher dietary exposure to PCBs. It has been estimated that the daily intake of non-dioxin-like PCBs from fish can reach approximately 80 ng/kg bw or even more in Baltic Sea fishermen (before taking into account the rest of the diet). Further, in many European countries, the daily intake of PCB by breastfed infants is significantly higher (per kg bw) than that of adults and adolescents (98).

Thus, there are still subpopulations in the general population with rather high plasma/serum concentrations of PCBs. For example, a comparison between Inuit women (from Greenland) and Swedish men showed that the levels of many PCB congeners were higher in the Inuits (Table 8). Yet, overall, it can be stated that the PCB body burdens in humans have decreased, as evidenced by lower levels reported in human adipose tissue, blood serum and breast milk, although a recent study on background levels of PCBs in the US population indicate that lower chlorinated (less than five chlorines) PCB serum levels have not changed considerably during the last decades. The slow reduction results from the constant feed of degraded and metabolised higher chlorinated PCBs (19, 178).

A mean PCB level of 146 ng/g lipid (range 30–402 ng/g lipid) in breast milk (PCBs 28, 52, 101, 105, 118, 138, 153, 156, 167, 180) was indicated in a Swedish study covering the period 1996–2003 (273 primiparous mothers). The highest mean values were found for PCBs 153, 138 and 180 (62, 31 and 29 ng/g lipid, respectively), whereas PCB 28 showed the largest variation in levels (0.3–307 ng/g lipid). Mean

Table 8. Mean plasma/serum levels of PCBs in different groups in the general population, i.e. Inuit women (77) and Swedish men (133).

PCB congener number	Inuit women, n = 153, age 49–64 years Plasma [a] PCB levels, ng/g lipid		Swedish men, n = 115, age 41–75 years Serum [b] PCB levels, ng/g lipid	
	GM	Range	AM	Range
PCB 28	7.7	nd–111	5.8	< 2.0–78
PCB 52	7.3	nd–80	4.2	< 2.0–16
PCB 99	88	9.3–295	-	-
PCB 101	8.9	nd–37	4.2	< 2.0–18
PCB 105	22	nd–78	6.6	< 2.0–28
PCB 118	122	20–372	42	4.3–143
PCB 138	418	71–1 385	142	3.1–335
PCB 153	579	94–1 993	294	23–627
PCB 156	77	11–296	23	7.9–50
PCB 167	-	-	10	< 2.0–30
PCB 170	132	20–606	-	-
PCB 180	351	58–1 709	216	71–480
PCB 183	42	7.4–160	-	-
PCB 187	164	24–660	-	-
Σ PCBs	2 051	341–7 384	-	-

[a] Samples from the year 2000.
[b] Sampling year was not given, but the study was published in the year 2000.
AM: arithmetic mean, GM: geometric mean, nd: not detected, -: not analysed.

values for the mono-*ortho*-PCBs decreased in the following order: PCB 118 (12 ng/g lipid) > PCB 156 (4.7 ng/g lipid) > PCBs 105, 167 (1.4 ng/g lipid). The decline in average level for different PCBs was about 5–10 % per year (238).

A substantial reduction of background PCB exposure between the mid 1990s and the early 2000s has also been indicated in Swedish men. Sixty % lower PCB levels in plasma (geometric means of lipid-adjusted PCB concentrations for the sum of 7 PCBs) were observed in a control group of construction workers compared to a group of historical controls (construction material industry and food industry workers). The mean plasma level (sum of PCBs 28, 52, 101, 118, 138, 153, 180) was 230 ng/g lipid (range 90–1 100) or 0.8 µg/l (range 0.4–2.0) in the samples from 2002, whereas the lipid-adjusted mean value in the historical control group was 580 ng/g lipid (354) (see Section 6.2).

In a study from 2007, serum concentrations of around 110 PCBs (from di- to decachlorinated congeners) in 87 Koreans (25 incinerator workers, 52 residents nearby and 10 residents not near the incinerator) were reported (or not detected). Arithmetic means of total PCB and dioxin-like PCB concentrations increased with age (stratified age groups, 21– > 50 years) and were 110–421 ng/g lipid and 2.6–10.8 pg TEQs/g lipid. Penta-, hexa- and heptachlorinated congeners contributed to more than 80 % of the detected total PCBs. The most abundant congeners were PCB 153 (mean value: 54.9 ng/g lipid), PCB 138/163 (34 ng/g), PCB 180 (28.4 ng/g), PCB 187 (12.3 ng/g) and PCB 118 (9.6 ng/g), all of which contributed to approximately 57 % of total PCBs. PCB 118 contributed to more than 50 % of the dioxin-like PCBs. The mean concentration of PCB 126 was 47 pg/g lipid. Several congeners (PCBs 12, 14, 21, 23, 36, 39, 42, 50, 54, 62/65, 69, 75, 104, 106, 107, 109, 116, 140, 143, 145, 150, 160, 161, 173, 182, 186 and 192) were not detected in any samples (287) (see Section 6.2).

In a meta-analytical approach, 37 articles published from 1990 to 2003 on PCB concentrations in blood, serum and plasma of subjects in different countries belonging to control groups or to reference groups of non-exposed individuals were selected and analysed. In total, 16 studies were selected for final analysis (number of determined congeners and dioxin-like congeners are only stated in five of these). In order to standardise the presentation of results, all the data were expressed as weight/volume. Thus, data reported as µg/g lipid (in plasma/serum) were transformed to µg/l plasma/serum considering a standard concentration of total lipids of 646 mg/100 ml serum, as suggested by Akins *et al* (4). The mean-median values of total PCBs varied between 1.2 and 8.3 µg/l plasma/serum in males and between 2.7 and 5.2 µg/l in females. The range was 0.9–56 µg/l for total PCBs and 0.2–2.4 µg/l for PCB 153 (259).

In Germany, the reference values (95th percentile of the pooled data) for the sum of the indicator congeners (PCBs 138, 153, 180) given by Kappos *et al* (1998) varied from 3.2 to 12.2 µg/l in plasma and 2.5–6.8 µg/l in whole blood (increasing with age). The mean values for the sum of PCBs in the age group 36–45 years were 3.8 µg/l in plasma and 2.1 µg/l in whole blood. Only samples after 1994 were taken into account. According to the authors, some caution is indicated since part of the data had been obtained by non-random sampling (203). Heudorf *et al* suggested new provisional reference values based on PCB plasma levels analysed in Germany

in 1998. The 95th percentiles in different age groups (18–65 years) were 3.0–9.4 µg/l for the PCB sum, 1.0–2.9 µg/l for PCB 138, 1.3–4.0 µg/l for PCB 153 and 0.9–3.3 µg/l for PCB 180. Mean values in the same age groups were 0.9–4.1 µg/l for the sum of the PCBs. The PCB compounds 28, 52 and 101 were below the detection limit in all blood samples (172). The German human biomonitoring commission presented reference values in whole blood (95th percentile) for different age groups (18–69 years) for PCB 138: 0.4–2.2 µg/l, PCB 153: 0.6–3.3 µg/l, PCB 180: 0.3–2.4 µg/l and for the sum of these PCBs: 1.1–7.8 µg/l, based on a German environmental survey performed 1997/1999 (347).

In Finland, an upper reference limit value of 3 µg/l serum has been set for the general population (254). This value has been estimated for the sum of 8 PCB congeners (PCBs 28, 47, 52, 74, 101, 138, 153 and 180) with 3–7 chlorine atoms in the molecule. The reference limit is not adjusted to the age of the persons investigated. Re-evaluation of the reference limit value is, however, under way (295).

6.1.2 Exposure in PCB-contaminated buildings (e.g. schools and office buildings)

Some exposure to PCBs may occur through dermal contact (soil and house dust) and inhalation of ambient and indoor air (269). PCB exposure in buildings is most likely the result of volatilisation, since levels of PCB on dust particles are very low compared to the gaseous phase (98). Sources of PCBs are e.g. sealants, paints, capacitors of fluorescent lamp ballasts, coatings or ceiling tiles (211). The congener pattern in air depends on the PCB source. For example, some Aroclors contained large amounts of mono- and dichlorinated congeners, whereas other Aroclors contained little or none (Table 6). However, only a weak influence of PCB contaminated air on the total PCB blood level was found in several studies, because the concentration of the low-chlorinated and more volatile PCBs (e.g. PCBs 28 and 52) in blood was still low (despite an increase) compared to the mean PCB blood concentration caused by food intake (125, 157, 349).

PCB levels of 10–20 µg/m^3 have been reported in a number of schools in Germany (98), although it has been stated that typical concentrations range between 0.5 and 10 µg/m^3 (125). Blood or plasma PCB levels in teachers and employees in commercial buildings are presented in Table 9.

Data on dioxin-like PCBs in indoor air of buildings with PCB containing materials are very limited (162). However, Kohler *et al* measured the PCB levels in indoor air in four Swiss public buildings containing joint sealants with PCBs and in one PCB contaminated industrial building (211). All dioxin-like PCBs and six indicator congeners (PCBs 28, 52, 101, 138, 153, 180) were measured. In the four public buildings, the sum of the latter multiplied by 5 gave a total PCB value of 0.7–4.2 µg/m^3. The most abundant of the indicator congeners were PCBs 28, 52 and 101. The most common dioxin-like congeners were PCB 118 (≤ 0.010 µg/m^3) and PCB 105 (≤ 0.0044 µg/m^3). The level of PCB 126 was below the detection limit in three of the buildings (0.000014 µg/m^3 in the fourth building). In the contaminated industrial building, the levels of PCBs 28, 52, 101, 138, 153 and 180 were 1.1, 1.2, 0.24, 0.03, 0.03 and 0.004 µg/m^3, respectively, giving a total PCB value of 13 µg/m^3 (six congeners × 5). The most abundant dioxin-like congeners were PCB 118 (0.066 µg/m^3) and PCB 105 (0.021 µg/m^3). The level of PCB 126

Table 9. Plasma or blood PCB levels in teachers in schools and employees in commercial buildings.

Facility or work	Country Year [a]	No. of subjects	Sample matrix	No. of congeners analysed	PCB level, µg/l		Reference
					Exposed, mean (range)	Controls, mean	
Commercial building	Germany 2002	583 exposed	Plasma	PCBs 28, 52 and 101	0.14 (0–0.68) 0.11 (median)	-	(45, 46)
				PCBs 138, 153 and 180	2.48 (0.28–9.72) 2.16 (median)		
				All 6 PCBs	2.65 (0.3–9.95) 2.32 (median)		
Schools	Germany 1997	18 exposed 11 controls	Blood	8 including			(349)
				PCB 28	0.24	0.03	
				PCB 52	0.07	0.03	
				PCB 101	0.02	0.01	
				PCB 138	0.70	0.52	
				PCB 153	0.96	0.77	
				PCB 180	0.62	0.63	
Schools	Germany 1994–1995	96 exposed 55 controls	Blood	6 [b] including			(125)
				PCB 28	0.05–0.10	0.04	
				PCB 138	0.66 [c]		
				PCB 153	0.95 [c]		
				PCB 180	0.70 [c]		

[a] Year of sample collection.
[b] One school also analysed all dioxin-like PCBs except PCB 81.
[c] Including controls.

was very low (0.000043 μg/m^3). It was stated that levels of dioxin-like PCB expressed as TEQs correlated well with the total indoor air PCB concentration and that a concentration of dioxin-like PCB of 1.2 pg TEQs/m^3 corresponds to a total PCB level of 1 μg/m^3 (211).

A survey on PCB congener levels in indoor air collected in 384 rooms of 181 public buildings, mainly schools, in Germany indicated that some low-chlorinated PCBs exhibited the highest concentrations (e.g. maximum values for PCBs 8, 18, 28, 31, 52 and 101 were 0.11–0.31 μg/m^3). The sum of the six indicator congeners (PCBs 28, 52, 101, 138, 153, 180) multiplied by 5 gave about 2 μg/m^3 of total PCBs as a maximum value. The 12 dioxin-like PCBs and PCDDs/PCDFs were also determined in four of the buildings. PCB 118 was by far the dioxin-like PCB occurring at the highest level and the congeners 118, 126 and 156 accounted for 85–95 % of the PCB-TEQs. TEQs of mono-*ortho* PCBs were 2–4 times higher than TEQs of non-*ortho* PCBs. Total TEQs (PCB + PCDD/PCDF) ranged from 0.4–5.9 pg/m^3 (162).

Teachers' exposure to PCBs in three contaminated German schools was assessed by monitoring PCB compounds in air and blood. Maximal indoor air values for total PCBs (six indicator congeners × 5) ranged from 1.6 to 10.7 μg/m^3 and mean values were 0.6–7.5 μg/m^3. PCBs 28 and 52 contributed to almost 90 % of the sum of the six indicator congeners in two schools, whereas PCBs 101, 138 and 153 dominated in one school. One school was also analysed for dioxin-like congeners with a maximum total level of 0.012 μg/m^3 and 12 pg/m^3 as an estimated sum of TEQs. No increase in blood levels could be detected for PCBs 138, 153 and 180 in exposed teachers compared to controls, whereas school specific differences were found for PCBs 28 and 101 (PCB 52 could not be evaluated). Mean PCB 28 blood concentrations were 0.05–0.1 μg/l in the three schools and 0.04 μg/l in the control group (with a considerable inter-individual variability). The blood levels of PCB 101 were 0.08 μg/l in one school and 0.04 μg/l in controls (125).

In a later German study, the effect of a heavy indoor air PCB contamination (up to 12 μg/m^3 for PCBs 28 and 52, respectively) on PCB blood levels of teachers (the six indicator congeners, PCBs 126, 169) was investigated. Blood analysis showed increased levels of PCB 28 (0.24 vs. 0.03 μg/l), PCB 52 (0.07 vs. 0.03 μg/l) and PCB 101 (0.02 vs. 0.01 μg/l) compared to a control group, but this increment was small compared to the total PCB load. A rough estimation suggested that this increase elevated the total PCB blood concentration of about 13 %. There were only minor differences (values in the range of the usual background concentration) between the groups regarding PCBs 138, 153 and 180. Moreover, blood lipid analyses revealed only slight differences in non-*ortho* PCBs (PCB 126: 156 vs. 132 pg/g lipid, PCB 169: 117 vs. 96 pg/g lipid) (349).

In a study of 583 subjects who had worked 1–40 years in a German commercial building with PCB contamination from insulation material and elastic sealing compounds, plasma samples (from 2002) were analysed for six indicator congeners (PCBs 28, 52, 101, 138, 153, 180). The mean PCB sum was 2.6 μg/l (maximum 10 μg/l). The mean sums for PCBs 138–180 and for PCBs 28–101 were 2.5 μg/l (maximum 9.7 μg/l) and 0.14 μg/l (maximum 0.7 μg/l), respectively. The median air concentrations in the building were 0.11 (PCB 28), 0.125 (PCB 52), 0.011

(PCB 101) and < 0.002 μg/m^3 (PCBs 138, 153, 180). The median sum of PCBs was given as 1.28 μg/m^3 (45).

In a Finnish study, the mean serum PCB concentration of 24 residents of PCB-containing buildings (sum of PCBs 28, 52, 77, 101, 118, 126, 138, 153, 169, 180) was 2.1 μg/l (range 0.95–4.1), whereas the mean value in a control group was 1.8 μg/l (range 0.23–12.6) (298).

In a Swedish study, some 30 PCB congeners were detected in blood samples from 21 inhabitants of flats in PCB-containing buildings, although only 15 could be quantified in all samples. Most of these congeners were only slightly elevated compared to controls (median levels were generally < 2 times higher, 3 times higher for PCB 74), but the concentrations of the two low-chlorinated PCBs 28 and 66 were several times higher (30 and 8 times). Total PCBs was 434 ng/g lipid, compared to 226 ng/g lipid in controls, as median concentrations in blood (198).

6.2 Occupational exposure

In occupational settings, inhalation is a major exposure route to PCBs (18, 19, 188), at least if respirators are not used, but dermal exposure as well as ingestion of PCBs have been demonstrated and may be of importance (252, 299). Although production of PCBs has ceased, occupational PCB exposure may still occur during handling of waste and as a result of recollecting electrical equipment that contains PCBs. In the US and Canada, many PCB transformers and PCB capacitors may still be in use and those who repair and maintain that equipment and those in the reclamation industry responsible for disassembly of PCB-containing transformers/capacitors are considered to have the highest potential for exposure. Exposure to PCBs may also occur when renovating and demolishing buildings (19, 212, 321). A large building can contain up to 100 kg of PCBs and workers are exposed to PCB-containing dust especially while grinding the old PCB-contaminated seam. When PCBs spread as dust particles, the congener pattern is similar to that determined for the equivalent sealant (299, 378). However, occupational exposure may also be due to PCB vapour emission, whereby the congener pattern in air is dominated by lower chlorinated congeners (98, 125, 351). The content of lower chlorinated congeners differs considerably between PCB mixtures (Table 6). The PCB level in serum or plasma can be used as a measure of the combined exposure of PCBs (from air, food etc.). PCB levels in serum, plasma or whole blood in some occupationally exposed groups are shown in Tables 10–12. For data on occupationally exposed teachers and employees in commercial buildings, see Section 6.1.2 and Table 9.

In a Swedish study, Sundahl *et al* evaluated renovation workers' exposure to PCBs. Air was sampled in the breathing zone of the workers during exchange of PCB-containing elastic sealants with PCB free materials. Measurements included seven indicator congeners (PCBs 28, 52, 101, 118, 138, 153 and 180). The pattern of the PCBs in the workplace air was different from that of the sealant and contained higher levels of lighter components. For air samples, a conversion factor of 6 was used to obtain the total PCB concentration from the sum of four congeners (PCBs 28, 52, 101 and 138). The total PCB concentrations in the workplace air at

the beginning were generally above 10 µg/m^3 (up to 120 µg/m^3). Later, when the techniques were optimised to take better care of dust and gases produced during the cutting and grinding etc., the levels were below or close to 10 µg/m^3 (378).

Workers in Finland replacing mastic sealants in prefabricated houses have also been found to be exposed to PCBs (213). The concentrations of PCB congeners 28, 52, 77, 101, 138, 153 and 180 in samples taken from the breathing zone of six workers were low, ranging from not detected to 8.7 µg/m^3. The four higher chlorinated congeners were found in higher levels than the less chlorinated PCBs, but correlations between air and serum levels were noted only for PCB 28 ($r = 0.70$) and PCB 52 ($r = 0.80$). In serum samples from 22 workers, the mean (range) total PCB concentration (sum of 24 PCBs) was 3.9 µg/l (0.6–17.8) as compared to 1.7 µg/l (0.3–3.0) in controls. Most of the PCB burden was due to more highly chlorinated congeners (> 4 chlorines) with a mean value of 3.5 µg/l (1.4 µg/l for controls). Further, serum levels of the sum of the 10 most abundant PCB congeners in elastic polysulphide sealants were 2–10 times higher in samples taken in the autumn after the renovation season than in samples from the same workers ($n = 5$) taken in the spring. The difference was explained by higher concentrations of PCBs 118, 138, 153 and 180. The authors concluded that some PCB exposure took place despite "appropriate" working equipment and personal protection (213).

PCB exposure during the removal of old sealants has also been assessed in a Finnish study by Priha *et al*. In the calculations, inhalation, dermal and ingestion exposures were considered as possible exposure pathways and US Environmental Protection Agency (EPA) risk assessment models were used. The PCB profile of the studied sealant samples (10 congeners were determined) closely resembled that of Aroclors 1260 or 1254. The major congeners found were PCBs 101, 138, 153 and 180 (Aroclor 1260 type) and PCBs 52, 101, 118, 138 and 153 (Aroclor 1254 type). PCBs spread as part of demolition dust and the congener pattern was similar to that determined for the equivalent sealant. The PCB levels and the total inhalable dust levels during the removal and grinding of sealants were measured in the breathing zone (outside the mask) of 14 workers (16 measurements). The median total inhalable dust level was 6.4 mg/m^3 (range < 0.1–309) and the median total PCB concentration calculated as Aroclor 1260 or 1254 was 26 µg/m^3 (range 6–803). The authors stated that the estimated exposure of the workers (all exposure routes) was about 10-fold higher than that of the general population (average dietary intake of PCBs 0.02 µg/kg bw/day). However, the serum PCB levels for the workers were only 3–4 times higher. According to the authors, exposure via inhalation is reduced by at least a factor of 10 when respirators are worn appropriately during dusty work operations and they suggested that their risk calculations therefore overestimated the real exposure (299).

In a Swedish study (354), the overall plasma PCB level in 36 abatement workers with at least 6 months experience of PCB removal from old sealants in the two previous years (2000–2001) was approximately twice as high as in a control group of 33 matched construction workers without occupational PCB exposure. The geometric mean levels expressed as the sum of 19 PCB congeners (tri- to heptachlorinated) were 2.3 µg/l (range 0.56–7.8) vs. 0.9 µg/l (0.45–2.2) or 580 ng/g lipid (160–2 200) vs. 260 ng/g lipid (110–1 200) as lipid-adjusted values. Mean levels

expressed as the sum of seven indicator congeners (PCBs 28, 52, 101, 118, 138, 153 and 180) were 1.6 µg/l (0.4–4.9) vs. 0.8 µg/l (0.4–2.0) or 410 ng/g lipid (120–1 800) vs. 230 ng/g lipid (90–1 100) as lipid-adjusted values. The highly chlorinated congeners PCB 153, 138 and 180 dominated in plasma in both exposed individuals and controls, and the geometric mean quotients did not differ considerably between the groups. Geometric means (exposed vs. controls) were 0.51 vs. 0.29 µg/l (PCB 153), 0.46 vs. 0.21 µg/l (PCB 138) and 0.35 vs. 0.24 µg/l (PCB 180). However, there were much higher levels of many less chlorinated PCBs in the exposed workers than in the controls (Figure 2). PCBs 66 and 56/60 were clearly elevated in the exposed group with geometric means of 0.065 vs. 0.0028 µg/l and 0.036 vs. 0.0012 µg/l. The dioxin-like PCBs 105 and 118 had mean values of 0.034 and 0.11 µg/l (0.0061 and 0.033 µg/l in controls). A follow-up of 25 workers after 10 months of additional exposure showed that the overall PCB burden in plasma was practically unaltered. For some congeners, notably PCBs 44, 47, 52, 70, 87, 95, 101 and 110, significant reductions were seen, but the contribution of these PCBs was limited. Subjects reporting no use of respiratory protection (n = 5) showed an increase of 12 ng/g lipid in the sum of 19 PCBs (geometric mean) over the study period as opposed to the other workers (n = 20) who presented a slight decrease of 3 ng/g lipid. It was suggested that the higher total serum values among the abatement workers as compared to controls were secondary to historical exposure and probably explained by less stringent protection of the exposed group prior to the implementation of the current safety regulations. In the occupationally exposed group of abatement workers, the geometric mean value (sum of seven PCBs) was lower than in historical controls, although not significant after age adjustment (410 vs. 580 ng/g lipid) (354) (see also Table 20 in Chapter 12).

In a pilot study, Herrick *et al* investigated serum PCB levels and congener profiles among US male construction workers. A blood sample was collected in 2005 from 6 workers (two were retired) who had installed and/or removed PCB-containing caulking material from buildings. The referent group consisted of 358 men who were seeking infertility diagnosis from a hospital (2000–2003). The mean sum of 57 PCBs in serum for workers and referents were approximately 2.8 and 1.3 µg/l, respectively. Serum concentrations for the construction workers and the referents were highest for PCBs 118, 138, 153, 170 and 180 (approximately 50 % and 60 %, respectively, of the total PCB concentrations). Mean serum levels of the heavy congeners (PCBs 84–209) were 2.61 µg/l (range 0.79–8.33) in workers and 1.19 µg/l in referents. Further, the mean levels of the more volatile, lighter di-, tri- and tetrachloro-PCBs (PCBs 6–74) were higher among the construction workers than among controls with a mean (range) of 0.23 µg/l (0.15–0.38) vs. 0.09 µg/l. In the only subject involved in removing PCB caulk at the time of the blood sampling, the contribution of PCB congeners 16, 26, 28, 33, 60, 66 and 74 was markedly higher than in the other 5 workers. Generally, seven PCBs (PCBs 6, 8, 16, 26, 33, 37 and 41) comprised 60 % of the sum of the light congeners for the construction workers. It should be mentioned that the workers' mean serum value exceeded the reference mean by a factor of 5 or more for PCBs 6, 16, 26, 33, 37, 41, 70, 97 and 136 (169). Most of these congeners have not been measured in other studies of workers removing PCB caulk (e.g. (213, 423). The mean serum concentrations

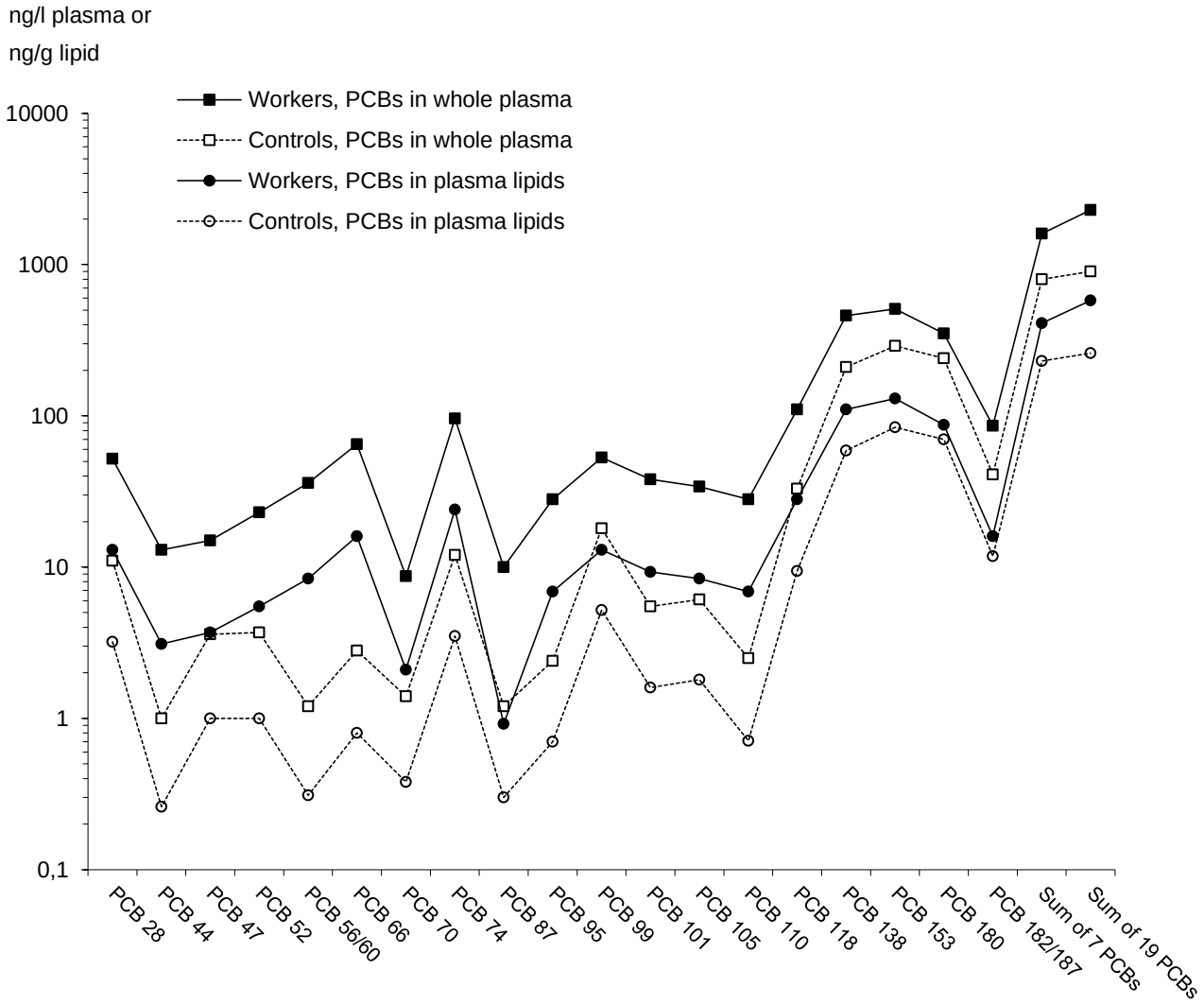

Figure 2. PCB levels in abatement workers and controls as reported by Seldén *et al* (354).

(µg/l) of the dioxin-like PCBs for workers and referents in the study by Herrick *et al* were as follows: PCB 157/201/177: 0.594 vs. 0.023, PCB 118: 0.136 vs. 0.076, PCB 156: 0.112 vs. 0.034, PCB 105/141: 0.032 vs. 0.019, PCB 167: 0.025 vs. 0.010, PCB 77/110: 0.009 vs. 0.005, and PCB 189: 0.007 vs. 0.004 (169).

The mean sum of 24 PCBs (including five dioxin-like congeners) found in the serum of 26 workers in a hazardous waste disposal plant in Finland was 3.4 µg/l (range 1.9–10.9) compared to 1.6 µg/l (0.3–3.0) for 21 controls. Serum levels (µg/l) were stated for some congeners and were as follows (workers vs. controls) PCB 28: ≤ 2.3 vs. ≤ 0.3, PCB 153: ≤ 2.0 vs. ≤ 1.1, PCB 180: ≤ 1.6 vs. ≤ 0.7, PCB 101: ≤ 1.4 vs. not detected, PCB 138: ≤ 1.3 vs. ≤ 0.6 and PCB 52: not detected vs. ≤ 0.2. The main PCB compounds found in waste incineration originated earlier from capacitor and transformer oils. Therefore, nine low-chlorinated PCB compounds (PCBs 8, 18, 28, 33, 44, 47, 66, 74, 101) have traditionally been measured in workers' serum to evaluate their exposure to PCBs. Nowadays, construction waste and contaminated soil containing mainly highly chlorinated congeners (PCBs 101, 118, 138, 153, 180) seem to be the main sources of PCBs in waste incineration in Finland. The mean proportion of PCB compounds with four or less chlorine atoms in this study was 20 % for workers and 14 % for the controls (212).

There was no difference in the plasma level of the sum of seven indicator congeners (PCBs 28, 52, 101, 118, 138, 153, 180) between 29 male workers at a hazardous waste incineration plant and 60 matched controls in a Swedish study. The mean values were 682 ng/g lipid (range 241–1 576) vs. 680 (234–4 523) ng/g lipid, respectively. However, the mean levels of PCBs 28 and 52 were significantly higher in exposed workers than in controls; 62 ng/g lipid (range 4–724) and 2.5 (0.5–13) ng/g lipid, respectively, for workers, and 3.3 ng/g lipid (0.7–29) and 1.3 (0.5–12) ng/g lipid, respectively, for controls. These results were quite concordant with the congener profile of the air monitoring analyses. Air samples from various locations within the plant showed air levels of 0.001–0.031 µg/m^3 for PCB 28 and 0.0005–0.008 µg/m^3 for PCB 52. The highest values for the other measured PCB congeners were 0.005 (PCB 101), 0.003 (PCB 153), 0.003 (PCB 138), 0.002 (PCB 118) and 0.0007 (PCB 180) µg/m^3. Estimated total PCB levels were 0.014–0.26 µg/m^3 at different locations (355).

The mean total PCB concentrations (PCBs 28, 52, 101, 138, 153 and 180) in pooled blood samples taken in 1997 in Spain from 14 workers at a municipal solid-waste incinerator, 93 persons living near an incinerator and 91 persons living far from an incinerator were 1.47, 2.11 and 1.99 µg/l, respectively. The sum of PCBs 138, 153, and 180 were 1.42, 2.06, and 1.94 µg/l, respectively. The workers experienced a slight decrease in PCB concentrations compared to the levels in 1995 before incinerator functioning (= background level). In 1995 and in 1997, PCBs 28 and 52 were not detected and PCB 101 was found at very low levels (138).

In a German study (published in 1992), no significant differences were found between 53 workers occupied in a municipal waste incinerator and 63 controls with respect to plasma levels of PCBs. The mean of the sum of PCBs 138, 153 and 180 was 6.33 µg/l for workers and 6.22 µg/l for controls. The levels of PCB 28, 52, and 101 were below the detection limits in both workers and controls (10).

In a Korean study from 2007, serum mean levels of total and dioxin-like PCBs in 25 workers at municipal solid waste incinerators were 215 and 15.6 ng/g lipid, respectively. Around 110 PCBs (di- to decachlorinated congeners) were analysed. No significant difference in congener or homologue distributions were found between the workers and residents nearby or > 10 km from the incinerator (287).

The mean serum PCB level from 17 employees at two adjacent US scrap metal dealers was 7.5 µg/l. The PCB concentrations were significantly related to eating lunch outside the lunchroom, which according to the author suggested hand-to-mouth contact as a source of exposure. Full-shift personal-breathing-zone air samples were collected for PCBs. No PCBs were found in any air or wipe samples taken by the Occupational Safety and Health Administration (OSHA). Bulk samples ranged from non-detectable to 265 ppm (257).

A mean serum PCB level of 7.4 µg/l (range 0.26–92) was obtained when 14 congeners (PCBs 52, 74, 99, 101, 118, 138, 146, 153, 177, 178, 180, 183, 194 and 201) were measured in samples collected 1996 in a cohort of US capacitor plant workers (n = 180) occupationally exposed to PCBs many years earlier (PCBs were used in the company 1952–1978). On average, these 14 PCBs accounted for almost 80 % of the total across all 38 PCBs measured and the highest levels were found for PCB 74 (123). A comparison between this cohort and a subgroup from the general population with extensive PCB exposure from food showed the differences in congener pattern in serum (Table 10).

A similar mean PCB level (measured 2003–2006) was reported for another population of capacitor workers (129 men, 112 women) with att least 3 months of employment 1946–1977 at US capacitor factories (351). The serum PCB levels (27 PCBs measured) were 7.5 µg/l (1 190 ng/g lipid) in men and 5.8 µg/l (860 ng/g lipid) in women, and 6.6 µg/l (1 020 ng/g lipid) in both genders combined (approximately 2-fold higher than in individuals who had not been working at the facilities). The geometric mean sums of the "light" PCBs (PCBs 28, 56, 66, 74, 99 and 101) were 2.8 µg/l (450 ng/g lipid) and 2.3 µg/l (340 ng/g lipid) in men and women, respectively, whereas the geometric means of "heavy" PCBs were 4.1 µg/l (650 ng/g lipid) and 3.2 µg/l (470 ng/g lipid), respectively. The total cumulative occupational exposure to PCBs (assessed by industrial hygienists) was significantly and positively associated with total PCB serum levels in 2004 after adjustment e.g. for age and body mass index. Cumulative exposure during the years that Aroclor 1016 was used (1971–1977) was most strongly related to the occupational "light" congeners, particularly PCB 74, although two "heavy" occupational congeners (PCBs 105 and 118) were also significant. The strength of an association for the years that Aroclor 1242 was used (1953–1971) was similar for both the occupational "light" and "heavy" congeners, and exposure to Aroclor 1254 (used 1946–1953) was significantly associated only with PCB 156. In general, the associations for "heavy" congeners were weaker in magnitude than those for the "light" PCBs. Serum PCB levels in 1976 (available for a subgroup) showed that PCB levels had decreased considerably during the 28-year interval (Table 11) (351).

Table 10. Proportions (%) of 14 PCBs in serum from former PCB exposed US capacitor workers and fish eaters (123).

PCB congener	Former capacitor plant workers [a] (n = 180)		Fish eaters [b] (n = 217)	
	Mean	Range	Mean	Range
PCB 52	0.1	0–5	0	0–0
PCB 74	33	0–87	4	0–12
PCB 99	6	0–19	3	0–12
PCB 101	0.1	0–3	0.3	0–15
PCB 118	9	0–28	7	0–23
PCB 138	16	3–35	29	0–47
PCB 146	2	0–34	2	0–7
PCB 153	19	0–40	24	15–43
PCB 177	0.2	0–2	0.4	0–3
PCB 178	0.3	0–19	0.4	0–4
PCB 180	10	0.3–33	22	12–61
PCB 183	1	0–5	1	0–4
PCB 194	2	0–15	3	0–8
PCB 201	3	0–22	5	0–15
Σ PCBs [c] (µg/l)	7.4	0.3–92	5.0	0.5–23

[a] PCBs used 1952–1978, serum samples taken in 1996.
[b] Heavy consumers of fish from the Great Lakes.
[c] The sum of 14 PCBs accounted on average for 78 % and 81 % of total PCBs (38 and 62 PCBs measured) in the cohorts of capacitor plant workers and fish eaters, respectively.
US: United States.

Table 11. Geometric means of PCB concentrations (wet weight, µg/l) in sera of former capacitor workers [a]. Adapted from Seegal *et al* (351).

PCB congener or summed score	Men (n = 33)		Women (n = 12)		All (n = 45)	
	1976	2004	1976	2004	1976	2004
Occupational PCBs						
PCB 28	12.13	0.11 [b]	9.23	0.49 [b]	11.27	0.17 [c]
PCB 74	8.67	1.74 [d]	5.71	4.89 [e]	7.75	2.29 [d]
PCB 105	0.68	0.12 [d]	0.36	0.24	0.58	0.14 [c]
PCB 118	1.69	0.32 [d]	1.77	0.91 [e]	1.71	0.42 [d]
PCB 156	0.24	0.21 [c]	0.15	0.30	0.21	0.23
Occupational summed PCBs						
Light PCBs (PCBs 28 and 74)	23.20	2.15 [c]	16.77	5.79 [b, e]	21.27	2.80 [d]
Heavy PCBs (PCBs 105, 118 and 156)	2.78	0.76 [d]	2.62	1.55 [e]	2.74	0.92 [c]
Total PCBs (light and heavy)	26.56	3.05 [d]	19.80	7.44 [b, e]	24.56	3.86 [d]
Occupational and non-occupational summed PCBs						
Light PCBs (PCBs 28, 74 and 56, 66, 99, 101)	28.82	3.58 [c]	20.76	6.98 [b,e]	26.41	4.28 [d]
Heavy PCBs (PCBs 105, 118, 156 and 138, 146, 153, 167, 170, 172, 174, 177, 178, 180, 183, 187, 199, 203)	9.01	4.42 [d]	9.27	7.29 [e]	9.08	5.05 [c]
Total PCBs (occupational and non-occupational)	40.37	8.38 [d]	31.62	15.05 [b,e]	37.82	9.80 [d]

[a] Employed at least 3 months 1946–1977.
[b] $p \leq 0.05$, paired t-test comparing 1976 and 2004 PCB concentrations.
[c] $p \leq 0.01$, paired t-test comparing 1976 and 2004 PCB concentrations.
[d] $p \leq 0.001$, paired t-test comparing 1976 and 2004 PCB concentrations.
[e] $p \leq 0.05$, t-test comparing 2004 PCB concentrations for males versus females.

Table 12. Serum, plasma or blood PCB levels in populations with occupational exposure.

Facility or work	Country Year [a]	No. of subjects	Sample matrix	No. of congeners quantified	PCB level, mean (range)				Reference
					µg/l		ng/g lipid		
					Exposed	Controls	Exposed	Controls	
Removal of PCB-containing caulk	US 2000–2005	6 workers, 358 controls	Serum	57 (incl PCBs 77, 105, 118, 156, 157, 167, 189)	2.83 (1.05–8.70) 2 [b] (median)	1.28 [b] (NG) 1 [b] (median)	-	-	(169)
Removal of PCB-containing sealants	Sweden 2002	36 workers, 33 controls	Plasma	19 (incl PCBs 105, 118)	2.3 (0.56–7.8)	0.9 (0.45–2.2)	580 (160–2 200)	260 (110–1 200)	(354)
Elastic polysulphide sealant renovation	Finland 1999–2000	22 workers, 21 controls	Serum	24 (incl PCBs 77, 105, 118, 126, 169)	3.9 (0.6–17.8) 1.9 (median)	1.7 (0.3–3.0) 1.5 (median)	-	-	(213)
Capacitor plant	US 1996 [c]	180 workers	Serum	14 (incl PCB 118)	7.39 (0.26–92)	-	-	-	(123)
Capacitor plant	US 2003–2006 [d]	241 workers	Serum	27 (incl PCBs 105, 118, 156, 167)	6.65 (NG)	-	1 020 (NG)	-	(351)
Transformer repair work	US [e]	35 current + 17 former workers, 56 controls	Serum	27 PCBs	Current exposure 53.7 (4.3–253) Past exposure 38.6 (1.5–143)	20.0 (0.5–181)	-	-	(114)
Waste incinerator	Finland 2001	26 workers, 21 controls	Serum	24 (incl PCBs 77, 105, 118, 126, 169)	3.4 (1.9–10.9) 2.9 (median)	1.6 (0.3–3.0) 1.5 (median)	-	-	(212)
Municipal waste incinerator	Korea	25 workers, 52 [f] + 10 [g] controls	Serum	110 PCBs (di- to decachlorinated) of which, sum of dioxin-like	-	-	215 15.6	281 [f], 114 [g] 21.7 [f], 9.7 [g]	(287)

Table 12. Serum, plasma or blood PCB levels in populations with occupational exposure.

Facility or work	Country Year [a]	No. of subjects	Sample matrix	No. of congeners quantified	PCB level, mean (range)				Reference
					µg/l		ng/g lipid		
					Exposed	Controls	Exposed	Controls	
Municipal waste incinerator	Germany	53 workers, 63 controls	Plasma	6 (PCBs 28, 52, 101, 138, 153, 180)	6.33 (1.80–36.8) 5.58 (median)	6.22 (0.99–20.91) 4.15 (median)	-	-	(10)
Municipal solid-waste incinerator	Spain 1997	14 workers, 93 [f] + 91 [g] controls	Blood	6 (PCBs 28, 52, 101, 138, 153, 180)	1.47 (NG)	2.11 [f] (1.45–2.88) 1.99 [g] (1.15–2.66)	-	-	(138)
Hazardous waste incinerator	Sweden	29 workers, 60 controls	Plasma	7 (PCBs 28, 52, 101, 118, 138, 153, 180)	-	-	682 (241–1 576)	680 (234–4 523)	(355)
Scrap metal dealer	US 1993	17 workers	Serum	Not stated	7.5 [h] (< 1–65.3)	-	-	-	(257)

[a] Year of sample collection.
[b] Calculated as the sum of the mean or median values for the group of light PCBs (sum of PCBs 6–74) and the group of heavy PCBs (sum of PCBs 84–209).
[c] Samples from 1996, but workers were exposed before 1978.
[d] Samples from 2003–2006, but workers exposed before 1978.
[e] Samples probably from the beginning of 1980s.
[f] Subjects living near an incinerator.
[g] Subjects living far from an incinerator.
[h] Excluding an outlier of 65.3 µg/l.
NG: not given, US: United States.

7. Toxicokinetics

7.1 Uptake and distribution

Humans can absorb PCBs by the oral and dermal routes and by inhalation. Inhalation exposure has been considered as a major route of occupational exposure to PCBs, although a significant contribution to the accumulation of PCBs in adipose tissue and serum from dermal exposure has been reported in some old studies e.g. on capacitor manufacturing workers (19, 233). Limited animal data indicate rapid and extensive uptake of lower chlorinated PCBs at inhalation exposure (180). Further, PCBs are well absorbed by experimental animals when administered orally (19, 382). Dermal uptake has also been documented (127, 128).

In a recent study in rats, it was estimated that 40 µg of a PCB mixture generated from Aroclor 1242 was inhaled, assuming a breathing frequency of 95 breaths/minute and a tidal volume of 1.5 ml/breath. The animals were exposed (nose-only) to 2 400 µg/m^3 of the vapour mixture, which consisted mainly (approximately 90 %) of mono-, di- and trichlorobiphenyls, for a total of 2 hours (two 1-hour exposures separated by a 1-hour break). The PCB load (body burden) at the end of exposure was calculated to be 33 µg, based on the amount of PCBs measured in five tissues (totally 5 µg/rat). The majority of the PCBs in blood at the end of exposure (mass percentage of total PCBs) were tri-, and tetrachlorinated congeners (approximately 35 % each) and pentachlorinated congeners (just over 25 %), whereas trichlorinated PCBs dominated in liver, lung, brain and adipose tissue and constituted approximately 50–60 %. Together these data indicated that inhalation was an efficient route of exposure for uptake of lower chlorinated PCBs, with an uptake of at least 80 % (180).

In the gastrointestinal tract, PCBs are absorbed by passive diffusion. Studies in rats have shown that all PCB congeners are well absorbed, with > 90 % absorption of the lower chlorinated congeners and somewhat lower absorption of the higher chlorinated congeners such as octachlorobiphenyls (98). Tanabe *et al* showed that the absorption efficiencies of individual congeners ranged from 66 % to 96 % in rats following 5 days of daily peroral administration of Kanechlor-300, -400, -500 and -600. The absorption efficiencies tended to be smaller as the number of chlorine atoms increased (382).

At dermal application, the degree of PCB chlorination has been shown to affect the rate and degree of penetration into skin and systemic absorption. Further, it has been suggested that the rate of absorption may be mediated, at least partly, by transdermal metabolism, mainly of the lower chlorinated congeners (127, 128). In rats, dermal penetration varied inversely with degree of chlorination of PCBs. ^{14}C-labelled mono-, di-, tetra- and hexachlorobiphenyls in acetone (0.4 mg/kg bw) were administered onto a 1 cm^2 clipped area on the backs of the animals and a stainless steel wire-mesh shield was glued over the dose site (the applied dose was left on the site for up to 48 hours). Distribution of radioactivity in the dose site and selected tissues was determined by serial sacrifice for up to 2 weeks. Systemic absorption was greatest for the mono- and dichlorobiphenyls, which penetrated the skin rapidly and were retained very little, whereas the more highly chlorinated PCBs remained

at the site of exposure (in the skin) and slowly entered the systemic circulation. Nearly 100 % of the applied dose of PCB 3 and 85 % of the dose of PCB 15 was systemically absorbed after 24 hours. Only around 35 % and 10 % of PCBs 47 and 155, respectively, had reached the systemic circulation at that time. The cumulative systemic absorption for the latter compounds was approximately 60 % (PCB 47) and 15 % (PCB 155) at 48 hours, and around 75 % (PCB 47) and almost 30 % (PCB 155) at 14 days (128).

In a recent review, the skin permeability coefficient (K_p) and flux values were calculated based on two studies by Garner *et al* (127, 128). K_p ranges (10^{-6} cm/hour) were 3–4 (PCB 3), 2–3 (PCB 15), 0.2–1 (PCB 47) and 0.2–0.4 (PCB 155). Reported flux values (µg/cm^2/hour) were 2.9–4.1 (PCB 3), 2.8–3.5 (PCB 15), 0.3–1.5 (PCB 47) and 0.4–0.8 (PCB 155) (197).

Some data concerning *in vivo* percutaneous absorption of PCBs in adult rhesus monkeys were reported by ATSDR. ^{14}C-labelled Aroclor 1242 was administered topically or intravenously and urinary and faecal excretion of radioactivity was measured for the next 30 days. Topical administration of Aroclor 1242 in soil, mineral oil, trichlorobenzene or acetone resulted in 14, 20, 18 and 21 % absorption of the administered dose, respectively (estimated in relation to data obtained at intravenous administration). Similarly, the *in vivo* percutaneous absorption of Aroclor 1254 in mineral oil and trichlorobenzene was 21 and 15 %, respectively. Further, after 15 minutes of dermal exposure, 93 % of the applied dose of Aroclor 1242 in trichlorobenzene was removed from skin by washing with soap and water, whereas at 24 hours, only 26 % of the applied dose was removed from the skin (19, 418).

In some old studies, inhalation exposure was considered to be a major route of occupational exposure to PCBs. Indirect evidence of absorption of PCBs by this route in humans was based on the fact that individual congeners were detected in tissues and body fluids of subjects exposed in occupational settings where air concentrations were also measured (19). ATSDR concluded that a maximum of 80 % of the levels commonly seen in adipose tissue of exposed capacitor workers may have been absorbed by the inhalation route, whereas a maximum of 20 % would have been derived from dermal or oral exposure. ATSDR reported that the concentration of PCBs in wipe samples from the face and hands of two employees varied from 0.05 to 5 µg/cm^2. A dermal exposure of 5 µg/cm^2 over the hands and face (ca 200 cm^2) or the entire body (ca 20 000 cm^2), assuming 100 % absorption into the main body reservoir (10 kg adipose), would represent 0.2–20 % of a 50 µg/g adipose level, which was commonly seen among capacitor workers (19, 425). On the other hand, a major contribution to total PCB body burden from dermal occupational PCB exposure rather than from inhalation has been suggested by some authors (233).

The highest concentration of most PCBs has been found in adipose tissue, but disposition of PCBs is affected by degree and position of chlorination (252). PCBs of low chlorination rapidly distribute to the tissues, whereas most higher chlorinated PCBs are more slowly distributed (128). The predominant PCB carriers in human plasma are in the lipoprotein fraction (19). PCBs tend to distribute first into highly perfused tissues such as liver and muscle and are then redistributed to tissues with high lipid content and low perfusion such as adipose tissue and skin

(128). The higher chlorinated congeners accumulate more extensively in fatty tissues, because of their great lipophilicity (422). However, calculated tissue:blood partition coefficients for liver, skin, muscles and fat for all 209 PCB congeners revealed that the partition coefficients decrease in the presence of adjacent unsubstituted *meta* and *para* carbons (252). Further, PCB levels in brain (lipid basis) are generally much lower than the levels found in e.g. subcutaneous fat, possibly due to the nature of the more polar brain lipids (19). In experimental animals, PCB 126 exhibits a dose-dependent liver retention by binding to the cytochrome P450 (CYP) isozyme CYP1A2 (94).

Due to its fat content, human milk can accumulate a large amount of PCBs. Human milk represents a good indicator for lipophilic unmetabolised PCBs stored in the body since fat is mobilised for the production of milk during lactation (152). Animal studies have revealed that large amounts of PCBs can be eliminated through lactation (119). In addition, offspring can be exposed to PCBs through transplacental transfer and concentrations of PCBs in humans are much higher in cord blood than in breast milk (19, 188). The PCB levels (PCBs 118, 138, 153, 180) in maternal and cord plasma have been shown to be similar when expressed on a lipid basis (otherwise higher in maternal than in cord plasma) (341).

The route of exposure may also be a relevant determinant of PCB distribution (252). Much lower blood concentrations and total excretion but much higher tissue concentrations were found on the 11th day post-dosing after dermal compared to intravenous exposure of swine to PCB 77 (304).

A study in ferrets demonstrated that the olfactory system may be a potentially significant portal for the entry of airborne PCBs, but further studies are needed to confirm this observation (19).

7.2 Biotransformation and excretion

The congener patterns in blood derived from food exposure differ from the patterns derived from occupational exposure due to the accumulation of high-chlorinated PCBs in the food chain (98, 252, 253). PCB profiles in human serum immediately following exposure reflect the profiles in the exposure sources, although selective metabolism and excretion begin to alter the congener profile within 4–24 hours (19). PCB congeners of low chlorination are quickly metabolised and eliminated, whereas most higher chlorinated PCBs are more slowly metabolised and eliminated (128). Higher chlorinated PCB congeners (4–10 chlorines) exhibit the greatest degree of resistance to metabolism. They may undergo several dechlorination steps to lower chlorinated metabolites before they are oxidised by hepatic enzymes (433). The rate of metabolism is also dependent on the positions of chlorination. PCB congeners with non-chlorinated *meta/para*-positions and chlorinated neighbouring *ortho/meta*-positions are rapidly metabolised (98, 188). Furthermore, the pattern and levels of CYP isoenzymes and other enzymes in the target tissue will have an influence on metabolism (19). Also, species differ in the ability to metabolise PCBs (48).

Metabolism of PCBs leads to formation of reactive intermediates with potential for adduct formation. The initial step in the biotransformation of PCBs involves oxi-

dation by CYP enzymes including epoxide formation and an alternative route for direct insertion of a hydroxyl group to PCB congeners less easily forming arene oxides (19, 98). Thus, PCBs are first metabolised to phenolic compounds, which can be further oxidised to dihydroxy metabolites. When the hydroxyl groups are *ortho* or *para* to each other (catechol or hydroquinone), oxidation by peroxidases to quinones via semiquinone intermediates may occur. These quinones and semiquinones are capable of reacting with DNA to form adducts, preferentially with guanine bases. It has been suggested that mainly PCB-derived *para*-quinones are involved in the major DNA adduction (433). However, the majority of all hydroxylated PCBs in humans are excreted in a non-conjugated form or further converted and excreted as glucuronide or sulphate conjugates. Only five major hydroxy-PCB congeners of all potential hydroxy-PCBs (approximately 50) are retained in the blood plasma bound to proteins, primarily transthyretin. The major hydroxy-PCB congeners in blood are present in concentrations about 5–10 fold less than the most persistent PCB congeners (98, 366).

PCB congeners with free *meta/para*-positions in at least one of the phenyl rings may form PCB methylsulphone metabolites in a multi-step pathway involving glutathione conjugates. These are excreted in the bile and undergo cleavage in the large intestine. Methylation of the resulting thiols followed by reabsorption and *S*-oxidation yields methylsulphonyl PCBs. Methylsulphone metabolites of PCBs have been detected in several organs (98, 252). The concentration of methylsulphonyl PCBs in human blood is low, but it is notable that some of these metabolites accumulate in a highly tissue- and cell-specific manner, with liver and lung as target tissues. The corresponding maternal PCB congeners are only present in trace concentrations or are non-detectable due to their rapid metabolism (98).

Biotransformation is necessary for the majority of PCB excretion, but limited excretion of parent PCBs does occur (19). Elimination of PCBs largely depends on the excretion of the polar hydroxylated metabolites in urine and faeces (98). Congeners like PCB 153 are not metabolised well and are excreted primarily as the parent compounds in the faeces (279). Generally, for higher chlorinated congeners such as penta- and hexachlorobiphenyls, the predominant route of excretion is via faeces, whereas lower chlorinated congeners are excreted mainly in urine (19). Another important route of PCB excretion is breast milk (19). There is significant elimination of unchanged PCB and its neutral metabolites (methylsulphonyl PCB) via breast milk (98).

In two studies on different occupational cohorts, the half-times for some PCB mixtures in serum were estimated, but congener specific PCB analysis was not conducted. The half-times were 1.8 and 2.6 years for Aroclor 1242, 3.3 and 4.8 years for Aroclor 1254 and 4.1 years for Aroclor 1260. According to ATSDR, these studies were well-designed and provided the best estimates of half-times of PCB mixtures following occupational exposure (19). In both studies, a more rapid elimination of PCBs was found in individuals with higher initial serum PCB levels.

Further, PCB elimination over a 3-year period was studied in 8 occupationally exposed women. Mean half-times (whole blood) for single congeners were 27.5 years (PCB 153), 16.3 years (PCB 138), 9.9 years (PCB 180), 8.4 years (PCB 74) and 3 years (PCB 28) (19). In a study of 39 individuals who had been exposed

Table 13. PCB half-times of former capacitor workers [a]. Adapted from (351).

PCB congener or summed score	PCB half-time (years) [a]		
	Men (n = 33)	Women (n = 12)	All
Occupational PCBs			
PCB 28	4.2	6.6 [b]	4.6
PCB 74	12.1	124.9 [c]	15.9
PCB 105	10.9	46.5	13.7
PCB 118	11.6	29.2 [b]	13.8
PCB 156	33.3	90.1	41.0
Occupational summed PCBs			
Light PCBs (PCBs 28 and 74)	8.2	18.2 [b]	9.6
Heavy PCBs (PCBs 105, 118 and 156)	14.9	37.2 [c]	17.8
Total PCBs (light and heavy)	9.0	19.8 [b]	10.5

[a] Calculated using the geometric means of data (collected in 1976 and 2004) expressed on a wet weight basis.
[b] $p \leq 0.01$, significant rank transformation analysis of variance test between men and women.
[c] $p \leq 0.05$, significant rank transformation analysis of variance test between men and women.

at two capacitor plants, PCBs were measured in serum from samples obtained in 1976 and 1983 (19). The half-times (geometric mean) were as follows: > 20 years (PCB 163), 12.4 years (PCB 153), 6–7 years (PCB 138), 5.8 years (PCB 118), 3.9 years (PCB 105), 3.3 years (PCB 99), 3.2 years (PCB 74) and 1.4 years (PCB 28).

Longer half-times were reported for some PCB congeners in a recent study. This is possibly due to the fact that serum PCB concentrations decrease in a non-linear, at least two-component, pharmacokinetic manner with the fastest decrease occurring shortly after exposure. The half-times of PCBs 28, 74, 105, 118 and 156 were estimated in serum of 45 former capacitor workers over a 28-year period (1976–2004). The data indicted a gender difference with women exhibiting half-times 1.5–10 times longer than men (Table 13). However, men had higher serum PCB levels in 1976 than women, which may explain the longer half-times in women (351).

8. Biological monitoring

Several investigators have examined whole blood, serum, plasma, breast milk, hair and adipose tissue in biomonitoring of PCB exposure. Caution is appropriate when comparing exposure estimates (even in the same matrix) or health effects reported by different investigators, because the approach for analysing PCBs in biological samples differs, which may have considerable impact on the reported PCB levels. There are several methods and approaches available for analysing PCBs in biological samples (Chapter 5) (19, 98, 188).

PCBs are stored at highest concentrations in adipose tissue, but because of the difficulties in acquiring adipose tissue samples, serum is considered as a more suitable matrix for occupational and environmental exposure assessment. Also plasma is often used as matrix (19, 20). Investigators typically express measurements on a wet weight basis (PCB per unit volume or weight of serum, e.g. µg/l serum or ng/g serum) or as lipid-standardised values where the serum concentrations are divided by serum lipids. The concentrations of lipophilic compounds like

PCBs in serum/plasma are often expressed as ng/g lipid in order to obtain biomarker values that reflect the body burden (31, 322, 345). Total serum lipids can be determined by gravimetric methods or easier as the sum of enzymatically determined lipid fractions (total cholesterol + triglycerides + phospholipids). Total serum lipids may also be predicted by three different formulae, requiring only values of serum cholesterol and triglycerides (31).

Authors report PCB concentrations as Aroclors, as sum of homologues or as individual congeners (188). PCB residue data in humans and animals suggest that tissue or body burdens of PCBs should be based on individual congeners or groups of congeners and not based on profiles of commercial PCB formulations (19). The most appropriate approach is to analyse for individual congeners, but the selection criteria for inclusion of congeners is very critical (183, 188). In most analytical investigations of PCBs, a limited number of congeners have been determined and there are different ways of calculating the total PCB concentration of a given sample based on this information (98). In a recent study, in which PCB congeners in the serum of volunteers were determined, it was found that total PCBs and dioxin-like PCBs highly correlated with PCBs 153 and 118, respectively. Thus, these two congeners could be satisfactory indicators for total PCBs and dioxin-like PCBs in human serum. In the case of TEQ concentrations, PCB 126 showed a high correlation and would be a suitable indicator for TEQ values (287).

The individual congeners found in humans do not reflect the original PCB mixtures (56). Overall, PCBs 138, 153 and 180 are the most consistently detected and quantitatively dominant congeners found in human tissues (19). The pattern of PCB congeners in adipose tissue will reflect long-term intakes and PCBs in breast milk largely reflects the concentrations of the congeners in adipose tissue (98). The six individual PCB congeners 28, 52, 101, 138, 153 and 180 are often used as indicators to assess environmental exposure but are not selected from a toxicological point of view. Sometimes a seventh congener, PCB 118, is included into the group of indicator PCBs (98, 423).

When analysing indoor air, samples are mostly dominated by the highly volatile, lower chlorinated PCB congeners 28 and 52, while the more persistent PCBs 138, 153 and 180 are normally of minor importance due to their lower volatility (98). In one study, a relation between the levels in serum and the levels found in the breathing zone was reported for PCB 28 ($r = 0.70$) and PCB 52 ($r = 0.80$) (213).

The congener pattern reported in human studies on environmental exposures differs substantially from those found in occupationally exposed workers (252, 253). Freels *et al* reported that PCB 74 was the most common congener in capacitor plant workers occupationally exposed to PCBs many years earlier (123). It has been suggested that this congener is particularly resistant to metabolism or a result of dechlorination of higher chlorinated congeners such as PCB 99 or 118 (427). Wingfors *et al* identified indicators of exposure related to the removal of old elastic sealants. The easily metabolised PCBs 44, 70 and 110 were found to be good markers of recent occupational exposure and the relatively persistent PCBs 56/60 and 66 of more long-term occupational exposure. The very persistent PCBs 153 and 180 were considered as markers of background (dietary) exposure. This set of indicator PCBs was suggested by the authors to be used instead of the

traditional set of seven indicator PCBs (see above) to trace occupational PCB exposure e.g. during the removal of PCB-containing sealants. Alternatively, the five PCB components (PCBs 44, 56/60, 66, 70 and 110) might be analysed in addition to the common indicator PCBs (423).

9. Mechanisms of toxicity

9.1 Introduction

PCBs exhibit a wide range of mechanisms of action that depend on the chlorine substitution pattern in the molecule. The presence or absence of chlorine in the *ortho* (2,2′,6,6′) positions is of particular importance. Four non-*ortho*-PCBs containing chlorines in the *meta* and *para* positions are dioxin-like and can have high-affinity binding to the Ah receptor, a cytosolic receptor protein present in most vertebrate tissues. Most, if not all, toxic and biological effects of the PCB congeners with high binding affinity to the Ah receptor are mediated through the Ah receptor. With an increasing number of *ortho* chlorines, the binding affinity to the Ah receptor decreases drastically. In this group of *ortho*-substituted congeners, only some mono-*ortho*-substituted PCBs exhibit some binding to the Ah receptor and thus some dioxin-like toxicity, but these mono-*ortho* dioxin-like congeners may act via non-Ah receptor-mediated mechanisms as well. Certain endpoints such as porphyrin accumulation, alterations in circulating thyroid hormone concentrations, neurotoxicity and carcinogenicity could arise by both Ah receptor-mediated and non-Ah receptor-mediated mechanisms. In addition, non-Ah receptor-mediated mechanisms of action may be shared by certain di-, tri- and tetrachloro-*ortho*-substituted PCBs. PCB congeners with two or more *ortho* chlorines do not exhibit any significant dioxin-like toxicity due to lack of binding to the Ah receptor, but multiple *ortho*-substituted PCBs have other pronounced mechanisms of action, e.g. resulting in effects on neurological development, dopamine levels and tumour promotion. However, in general, the more specific effects of multiple *ortho* PCBs are seen at considerably higher dose levels than the pronounced dioxin-like effects that are associated with some PCBs that are potent Ah receptor agonists (109, 166, 188, 402). The degree of dioxin-like toxicity (Ah-receptor mediated mechanisms) can be estimated by the TEF and TEQ concept (Chapter 2). Further, a relative potency scheme for estimating neurotoxic effects for non-dioxin-like PCBs based on e.g. interference with intracellular signalling pathways dependent on calcium homeostasis has been suggested (361).

9.2 Groupings of PCB congeners

Congener-specific analysis combined with the WHO TEF and TEQ concept may be useful for characterising dioxin-like health effects, although the TEFs at present are primarily intended for estimating exposure and risks via oral ingestion (19, 402). Other mechanism-based approaches involve grouping of PCB congeners with respect to their CYP enzyme induction properties, only or in combination with occurrence (Table 14).

Table 14. Type of induction of microsomal cytochrome P450 (CYP)-dependent mixed-function oxidases (MFOs) of some important PCB congeners (265).

Induction mechanism				
3-methylchol-anthrene-type (Group 1A)	Mixed type, common [a, b] (Group 1B)	Mixed type, uncommon [a, c] (Group 4)	Phenobarbital-type [b] (Group 2)	Weak or non-inducers [b] (Group 3)
PCB 77	*PCB 105*	PCB 37	PCB 87	PCB 18
PCB 126	*PCB 118*	*PCB 81*	PCB 99	PCB 44
PCB 169	PCB 128	*PCB 114*	PCB 101	PCB 49
	PCB 138	PCB 119	PCB 153	PCB 52
	PCB 156	*PCB 123*	PCB 180	PCB 70
	PCB 170	*PCB 157*	PCB 183	PCB 74
		PCB 158	PCB 194	PCB 151
		PCB 167		PCB 177
		PCB 168		PCB 187
		PCB 189		PCB 201

[a] Both 3-methylcholanthrene and phenobarbital inducers.
[b] Frequently found in the environmental samples and relatively abundant in tissues.
[c] Reported infrequently in environmental samples and in relatively low concentrations.
Dioxin-like congeners.

An alternative grouping that takes into account the biological action of PCBs was proposed by Wolff *et al* (426). PCB congeners were grouped as follows (congener number as designated by Ballschmitter and Zell, 1980 (25)):

Group 1: potentially oestrogenic
1A: not persistent, weak phenobarbital inducers
(PCBs 31, 44, 49, 52, 70)
1B: persistent, weak phenobarbital inducers
(PCBs 101, 174, 177, 187, 201),

Group 2: potentially antioestrogenic and immunotoxic, dioxin-like
2A: moderately persistent, non-/mono-*ortho*-substituted
(PCBs 66, 74, 77, 105, 118, 126, 156, 167, 169)
2B: persistent di-*ortho*-substituted
(PCBs 128, 138, 170),

Group 3: persistent, phenobarbital, CYP1A and CYP2B-inducers
(PCBs 99, 153,180, 183, 196, 203).

Another classification scheme for PCB grouping based on purported endocrine activity suggested by Cooke *et al*, 2001 included oestrogenic congeners (PCBs 4/10, 5/8, 15/17, 18, 31, 44, 47, 48, 52, 70, 99, 101, 136, 153, 188) and antioestrogenic congeners (PCBs 77/110, 105, 114, 126, 156 /171, 169) (52, 274).

Further, there are structure-based groupings, e.g. mono-ortho- and di-ortho-substituted congeners (63). Moysich *et al*, 1999, made three groupings based on degree of chlorination (272):

- lower chlorinated PCBs (di-, tri- and tetrachlorinated),
- moderately chlorinated PCBs (penta-, hexa- and heptachlorinated),
- higher chlorinated PCBs (octa- and nonachlorinated).

9.3 Enzyme induction

PCBs induce hepatic phase I and phase II enzymes to varying degrees. The congeners that show high-affinity binding to the Ah receptor such as non-*ortho* PCBs can be potent inducers of 3-methylcholanthrene-type CYPs like CYP1A1 and CYP1A2. Induction of 7-ethoxyresorufin-*O*-deethylase (EROD) activity is a marker of CYP1A1 activity (19, 188, 280). CYP1A1 is involved in the metabolism of steroid hormones and polycyclic aromatic hydrocarbons (PAHs) in humans and a result of induction of CYP1A1 is an increased capacity for bioactivation of PAHs (47, 348). In contrast, the PCBs that have an *ortho*-substitution pattern induce enzymes in the CYP2 and CYP3 families, which resemble the induction by phenobarbital. In this respect, the mono-*ortho* PCBs take an intermediate position, as they can induce enzymes from the CYP1 as well as the CYP2 and CYP3 families, a property that is generally lost for the di-*ortho*-substituted PCBs (188). Enzyme induction (especially for dioxin-like PCBs) leads to proliferation of the endoplasmic reticulum in the liver, resulting in increase in liver size and alteration in liver function (57). Type of induction of microsomal cytochrome P450 (CYP)-dependent mixed-function oxidases (MFOs) of some important PCB congeners are shown in Table 14.

9.4 Inhibition of body weight gain and porphyria

Activation of the Ah receptor leads to changes in gene expression and signal transduction. Changes in cell proliferation and differentiation, inhibition of body weight gain and porphyria appear to predominantly involve Ah receptor initiated mechanisms (19, 188).

9.5 Immune effects and cardiovascular effects

Dioxin-like PCBs may disrupt endothelial barrier function, activate oxidative stress-sensitive signalling pathways and induce subsequent proinflammatory events (interleukin (IL)-6), indicating a possible role in the pathology of atherosclerosis and cardiovascular disease. Induction of CYP1A1 and activation of nuclear factor kappa B (NFκB) have been proposed as critical mediators for an endothelial cell inflammatory response (164). Endothelial cell dysfunction via activation of CYP1A1 and increased cellular oxidative stress, and subsequent overactivation of the DNA repair enzyme poly(ADP(adenosine diphosphate)-ribose) polymerase and depletion of cellular NADPH (nicotinamide adenine dinucleotide phosphate) was indicated in a recent study. It was suggested that depletion of NADPH levels in endothelial cells would result in a decreased production of nitric oxide and reduced vasodilatation, which might predispose exposed individuals to development of hypertension and cardiovascular disease (163). Both coplanar and non-coplanar PCBs can cause endothelial cell dysfunction as determined by markers such as expression of cytokines and adhesion molecules (165). Exposure of vascular endothelial cells to environmentally relevant concentrations of PCB 153 induced gene networks implicated in the process of inflammation and adhesion (117).

PCBs can cause immunosuppression. *In vivo* immune defects include decreased thymic weight, reduced B cell numbers, reduced cytotoxic T-lymphocyte response and reductions in plaque forming cell response and immunoglobulin (Ig) M. The non-dioxin-like PCBs tested (e.g. PCB 153, 170, 180) were less potent *in vivo* than the dioxin-like PCBs (98).

Mechanisms of immunotoxic actions of PCBs that are independent of the Ah receptor, e.g. reduced lipopolysaccharide induced proliferative response in splenocytes, reduced antibody secretion and impaired neutrophil function, have been indicated *in vitro* (98). The results from studies on neutrophils suggest the involvement of an Ah receptor independent mechanism that involves increases in intracellular calcium, or, PCB effects on a signal transduction pathway that is dependent on calcium availability. Some studies indicate activation of phospholipase A2, release of arachidonic acid from triglycerides and production of prostaglandins as a probable mechanism (19).

9.6 Endocrine effects and effects on the retinoid system

PCBs cause alterations of several hormonal systems, including thyroid and sex steroids (267). Generally, dioxin-like PCBs are considered more potent than non-dioxin-like PCBs for such effects (346). The effects of the endocrine disrupting pollutants depend probably on changes induced in the production or metabolism of endogenous hormones (resulting in changed levels in the target tissues) and on the direct interaction of the pollutants with the hormonal receptors (95).

The planar PCBs 77, 126 and 169 (or their metabolites) and commercial mixtures that contain them (Arocolor 1254) seem to possess not only antithyroid but also some thyreomimetic properties in developmental studies. Since thyroid hormones, oestrogens and androgens play an important role in the development, PCB exposure during sensitive developmental periods may result in adverse effects on the growth and functional integrity of the organism, especially the brain (396). Changes in plasma levels of total thyroxine (T_4), free T_4 and total triiodothyronine (T_3) may e.g. be related to hypothyroidism in foetal and early prenatal life, which may result in profound effects on the developing brain including hearing deficits (346).

Animal studies suggest that PCBs can disrupt the production of thyroid hormones both in the thyroid and in peripheral tissues, interfere with their transport to peripheral tissues and accelerate the metabolic clearance of thyroid hormones (19). Disruption in thyroid hormone homeostasis occurs through mechanisms that transcend all congener groups of PCBs, thus appear to involve Ah receptor mediated as well as Ah receptor independent actions (19). One possible mechanism for dioxin-like PCBs is the induction of uridine diphospho-glucuronosyl transferase (UDP-GT), which catalyses the metabolic elimination of T_4 to T_4-glucuronide conjugate (19, 98, 346). Hydroxylated PCBs can inhibit type I deiodinase activity and have been found to act as inhibitors of T_2 sulphotransferase activity *in vitro* (366). Another mechanism includes inhibition of the binding of T_4 to transthyretin, although thyroxine-binding globulin is a more important T_4 plasma transport protein for humans than transthyretin and binds most PCBs very weakly or not at all. It would

appear therefore that plasma transport of T_4 is less sensitive to PCB exposure in humans than in rodents. Still, the effects on T_4 supply to the brain may be similar in humans and rodents due to the involvement of transthyretin in this process (19, 98, 346, 396).

PCB congeners and hydroxylated PCBs, especially mono- and dihydroxy-PCBs, have been shown to possess oestrogenic and antioestrogenic effects (19, 56). PCB-induced oestrogenic activities have generally been characterised as weak compared to the endogenous hormone 17ß-estradiol (19). The exact mechanisms of oestrogenic or antioestrogenic activities of non-dioxin-like PCBs are not fully characterised. The reported results are often contradictory, derived from data obtained in different *in vitro* and *in vivo* models (294). Oestrogenic and antioestrogenic effects can be mediated by binding to the oestrogen receptor and hydroxylated PCBs are postulated to be at least partly involved (19, 188). Interaction with the oestrogen receptor has also been observed after exposure to methylsulphone PCB metabolites (188). In addition to direct interactions with oestrogen receptors, other influences on oestrogenic mechanisms are possible. Human oestrogen sulphotransferase e.g., may be inhibited by hydroxylated PCBs and may thus increase the availability of endogenous oestrogens (396). Further, PCBs may cause increased metabolism and excretion of oestradiol because of enzyme induction of the phenobarbital type. Also, coplanar PCBs activate the Ah receptor and cause induction of CYP families that catalyse the metabolism of oestradiol. In addition to inducing CYPs, some of the PCBs and metabolites can directly inhibit these enzymes (56).

Some PCB congeners may increase gonadotropin-releasing hormone or produce effects beyond the receptor for gonadotropin-releasing hormone. PCBs may also affect production and release of luteinising hormone from the pituitary gland by mechanisms unrelated to oestrogenic action (188).

Furthermore, PCB congeners can be androgenic or antiandrogenic. In mice and rats, anogenital distance is an indicator of prenatal androgenisation (higher androgen level - longer anogenital distance) (396). Non-dioxin-like PCBs may interfere with the binding of testosterone to the androgen receptor, and the dioxin-like PCB 77 has been shown to lower testosterone levels in rats (98, 346).

Carpenter *et al* stated that the net activity of most PCB mixtures is to mimic the actions of oestrogen (57). Yilmaz *et al* suggested that low-chlorinated PCB mixtures such as Aroclor 1221 have oestrogenic properties, whereas high-chlorinated PCB mixtures such as Aroclor 1254 may exert antioestrogenic effects (430). The majority of the studies found that lower-molecular-weight PCBs may elicit oestrogenic activity both *in vitro* and *in vivo* (294). Among the congeners suggested as oestrogenic are PCBs 4/10, 5/8, 17, 18, 28, 31, 44, 47, 48, 49, 52, 66, 70, 74, 82, 95, 99, 101, 110, 128, 136, 179 and 188 (52, 89, 133, 274, 294, 411). Yet some of the lower chlorinated congeners (e.g. PCBs 8, 28, 31, 70, 101) were not oestrogenic at *in vitro* screening as reported by de Castro *et al* (89). The three most prevalent non-dioxin-like congeners, PCBs 138, 153 and 180, and other high-chlorinated non-dioxin-like PCBs (PCBs 170, 187, 194, 199, 203) have been reported to be antioestrogenic *in vitro*, but PCB 153 has also been reported as oestrogenic and PCB 138 as antiandrogenic (39, 133, 294, 411). The dioxin-like PCBs are generally considered as antioestrogenic (294).

PCBs have also been shown to decrease the aromatase activity in the brain of new-born male rats after maternal exposure. During critical developmental periods, changes in aromatase activity may result in changes in several brain regions, altering sex-dependent neurobehaviour (346). Still, any hormonal effect is likely to be species-, tissue, and developmental stage-specific (188).

Modulation of glucocorticoid synthesis has been observed *in vivo*. One possible explanation is inhibition of CYP11B enzyme activity in the adrenals by methylsulphone PCBs (188).

Decreased hepatic vitamin A stores have been found *in vivo* at peroral administration of some PCBs. Compared to TCDD, the hepatic vitamin A reducing potencies of PCB 126, PCB 77 and PCB 153 were 0.05, 0.0001 and 0.00001, respectively, in male rats (184). It has been suggested that the mechanism of vitamin A reduction involves both induction and inhibition of retinoid specific enzyme activities (227). Further, effects of PCBs on vitamin A can partly be explained by the fact that transthyretin forms a complex with the retinol binding protein (188).

9.7 Diabetes

The contribution of exposure to persistent organic pollutants (POPs) to the incidence of diabetes has received much attention in recent years. Carpenter stated that, although a specific mechanism is not known, most POPs induce a great number and variety of genes, including several that alter insulin action (58). Mechanistic studies have indicated effects of TCDD on the expression of genes implicated in type 2 diabetes (151). Insulin receptor substrate 1 (IRS-1) expression was significantly downregulated in cells treated with 17β-oestradiol and TCDD. IRS-1 interacts in the initiation of cellular functions regulated by insulin, including insulin-initiated cell signalling. This results in the transport of a glucose transporter protein (GLUT4) to the cell membrane. A decrease in intracellular IRS-1 with a subsequent decrease in function of GLUT4 results in insulin resistance and hyperglycemia in human cells (174). A link between dioxin-like compounds and diabetes through interaction between the Ah receptor and the peroxisome proliferator-activated receptor γ (PPAR γ)-mediated signalling pathways (PPAR antagonism) was suggested by Remillard and Bunce (307). Further, adipocytokines have been connected to obesity and insulin resistance, and it has been shown that TCDD may induce low-grade inflammation of adipose tissue and also downregulation of adiponectin, one of the major secretory products of adipose tissue known to augment the effects of insulin on glucose homeostasis (273). An interaction between PCB 153 and adiponectin in obese women was suggested in a recent small study, although it cannot be excluded that PCB 153 was only a biomarker of exposure to some other active pollutant. It was hypothesised that PCB 153 may downregulate adiponectin through induction of CYP2B (273). A PCB-stimulated increase of insulin release from insulinoma cells, in part due to an increase in intracellular free calcium, has been shown in animal models with PCB 47, PCB 153 and Aroclor 1254. This may play a role in the development of insulin resistance (110).

9.8 Bone effects

Several studies of wildlife suggest that organochlorines including PCBs can impair bone strength and alter bone composition (200, 241, 320). The underlying toxicological mechanisms are yet not fully understood (241, 320). Studies in Baltic seals have indicated that bone lesions may be associated with contaminant mediated vitamin D and thyroid disruption. However, antioestrogenic activity has been proposed as another possible explanation for bone effects of e.g. PCBs (200, 320).

9.9 Neurotoxicity

PCB mixtures, like different Aroclors, and single PCB congeners have been shown to directly affect neuronal cells (346).

Mechanistic studies *in vivo* and *in vitro* have shown that PCB congeners that are not effective Ah receptor agonists can affect components of the nervous system directly in at least four different ways by:

- altering intracellular concentrations of calcium by interference with intracellular sequestration mechanisms of calcium and increased activation of protein kinase C, thereby altering intracellular signal transduction pathways,
- inducing apoptosis subsequent to activation of the ryanodine receptor and increased production of reactive oxygen species (ROS). Cell death and increased ROS formation has also been mediated through the *N*-methyl-*D*-aspartate (NMDA) receptor,
- changing the levels of neurotransmitters such as dopamine and acetylcholine, the latter may be due to interference with PCBs on thyroid hormone levels, because cholinergic fibres are particularly sensitive to thyroid hormone deficiency, and
- increasing the release of arachidonic acid through mediation of phospholipase A(2) activity.

Many of these effects have also been observed with dioxin-like PCBs, although non-dioxin-like PCBs generally are more potent when tested in the same systems. Non-dioxin-like PCBs have been shown to be more potent in causing changes in the phosphokinase C signalling pathway and calcium homeostasis and in reducing dopamine levels in the brain. These endpoints are thought to be related to modulation of motor activity, learning and memory, neural damage and abnormal brain development (98, 346).

A reduced amount of NR1 subunit of NMDA receptors with a subsequent reduced function of the glutamate-nitric oxide-cyclic guanosine monophosphate (cGMP) pathway in cerebellum, leading to a decreased ability to learn, was observed after treatment with the non-dioxin-like PCBs 138 and 180. Further, an increase in extracellular γ-aminobutyric acid (GABA) in cerebellum with impaired motor coordination was seen after treatment with the non-dioxin-like PCB 52 (37).

Caudle *et al* investigated mechanisms by which PCBs may disrupt normal functioning of the nigrostriatal dopamine system in mice at administration of a 1:1 mixture of Aroclor 1254:1260. Upon analysis of all congeners present in the

brain, PCBs 95, 118, 138, 153, 170 and 180 were found at higher concentrations. Reduction in vesicular monoamine transporter 2 levels in the striatum was detected but no changes in striatal dopamine (and metabolite) levels. Also, a reduction in nigrostriatal dopamine transporter protein levels and function was seen. No influence on dopamine transporter protein levels in frontal cortex, hypothalamus and midbrain was found. The levels of other neurotransmitter transporters (e.g. for serotonin, epinephrine, glutamate) present in striatum and frontal cortex were not altered. The changes may represent a precursory event leading to deficits in dopamine levels and further damage to the dopaminergic system (60).

Also, learning could possibly be impaired by inhibition of nitric oxide synthase by *ortho*-substituted PCBs and their hydroxylated metabolites as well as hydroxylated metabolites of non-*ortho* PCBs (396).

Further, indirect influences via effects on steroids are possible because most transmitter systems such as serotonin, dopamine, acetylcholine and glutamate can be influenced by sexual hormones, and individual PCBs may have oestrogenic, antioestrogenic, androgenic or antiandrogenic activity (396). Both dioxin-like and non-dioxin-like PCBs as well as some hydroxyl metabolites have been shown to interfere with endocrine systems (sex-steroids, thyroid hormones) and with retinoids (metabolites of vitamin A), thereby acting on multiple endpoints. Through these mechanisms they impair neurological development and functioning, with dioxin-like PCBs more potent than non-dioxin-like PCBs (346). The effects may be due to PCB regulation of CYP oxygenases that activate or deactivate different steroid hormones, to interference of PCBs with the hormone receptor or with the hormone transport protein (346).

9.10 Genotoxicity and carcinogenicity

There is evidence that both Ah receptor dependent and independent mechanisms may be involved in PCB-induced cancer (19). Sandahl *et al* suggested that indirect effects on DNA, like DNA damage secondary to oxidative stress, may be the basis for the carcinogenic actions of PCBs (331). It has been suggested that the carcinogenic effects of both TCDD and phenobarbital may in part reside in the capacity of the induced CYP enzymes to leak oxidants and thus promote cell division and oxidative DNA damage (289).

Dioxin-like compounds do neither bind covalently to DNA, nor induce direct genotoxic effects, but might be indirectly genotoxic by increasing the formation of ROS (196). The indirect genotoxicity may be via an Ah receptor dependent induction of the CYP1 family (e.g. CYP1A1), which leads to an induction of oxidative stress (i.e. increased ROS formation and oxidative DNA damage). This is due to inefficient electron transfer during P450 metabolism or the production of redox active oestradiol metabolites as a result of CYP1 mediated oestrogen metabolism. The effects of dioxin-like compounds on hormone and growth factor systems, cytokines and other signal transducer pathways indicate that they are also powerful growth dysregulators (196, 280, 289).

Further, experimental evidence supports the hypothesis that lower chlorinated PCBs are metabolically activated to electrophilic species, which bind to DNA. The

reactive metabolites may result from arene oxides and/or catechol and *p*-hydroquinone species, which are oxidised to semiquinones and/or quinones. Formation of these oxygenated compounds is accompanied by production of ROS and oxidative DNA damage. The results raise the possibility that lower chlorinated PCBs may be genotoxic (19, 56, 98, 256). One major route to aneuploid cancer cells is through an unstable tetraploid intermediate, and in a recent study it was suggested that PCB 2 hydroquinone and PCB 3 hydroquinone may be involved in cancer initiation through induction of polyploidisation (122).

A general mechanistic hypothesis for PCB promotion of liver tumours involves indirect stimulation of cell proliferation following cell or tissue injury by reactive metabolites of PCBs. Alternatively, the cell injury could be caused by increased intracellular concentrations of other reactive species caused by an overall imbalance from PCB-induced perturbations of cellular biochemical processes, including induction/repression of enzymes and/or disruption of calcium homeostatic processes and signal transduction pathways (19).

A mode of action of PCB mixtures for cancer in Sprague Dawley rats was presented in a recent publication (49). The following steps were suggested: 1) PCB/TEQ accumulation in rat tissues, 2) PCB/TEQ repression of constitutive MFOs, 3) PCB/TEQ induction of other MFOs, 4) MFO-mediated formation of redox-cycling quinones (RCQs), 5) RCQ-mediated formation of $O_2^{\cdot -}$, 6) $O_2^{\cdot -}$ dismutation to H_2O_2 and 7) H_2O_2-mediated mitotic signalling, resulting in the proliferation of spontaneously or otherwise initiated cells to form hepatic tumours as in tumour promotion. In this cancer process, tumour growth and development is controlled by the net activity of multiple MFO-RCQ-ROS mitotic signalling cascades. Glutathionylated oestrogen catechols (RCQs) were identified in rat livers (49).

Inhibition of apoptosis of preneoplastic cells, a mechanism of TCDD promotion, has been observed after PCB exposure (98). However, PCB promotion of tumours does not appear to be solely an Ah receptor mediated process. Tetra- and hexachlorinated PCBs that are not Ah receptor agonists have been shown to be potent inhibitors of intercellular communication *in vitro* and/or to promote liver tumours *in vivo* (19, 188). In addition, sulphonated and hydroxylated PCB metabolites have been reported to inhibit gap junction intercellular communication *in vitro* (98, 204, 256). Machala *et al* showed that the strongest inhibition potencies were found for some persistent high-molecular weight 4-hydroxy-PCBs (4-OH-PCB 146, 4-OH-PCB 187), but also that several low-molecular weight hydroxylated PCBs inhibited intercellular communication, which is potentially associated with promotional effects (256).

The fact that PCBs may cause immunosuppression may at least in part explain their carcinogenic actions (56).

10. Effects in animals and in vitro studies

The precise composition or the content of PCDFs and other impurities in commercial PCB mixtures is seldom known, although the approximate homologue composition is well-known (Table 6, Chapter 4), and even minor contamination

(in the range of 0.1 %) with potent dioxin-like compounds may be sufficient to explain (or have a significant impact on) the observed adverse effects (98, 188, 402). However, it has been suggested that PCB mixtures containing a higher percentage of moderately chlorinated homologues (tetra-, penta- and hexachlorinated congeners) are more toxic than mixtures containing a lower proportion regarding effects related to Ah receptor binding and disruption of calcium homeostasis. Accordingly e.g., the Aroclors 1242, 1248 and 1254 would be more toxic than Aroclor 1221 (a lesser chlorinated mixture) and Aroclors 1262 and 1268 (more heavily chlorinated mixtures) (361). Yet, there might be other mechanisms of importance not taken into consideration in the above cited assessment of toxicity of PCB mixtures.

For technical PCB mixtures, no effects were seen in rodents and monkeys in the low mg/kg bw/day range for a number of toxicological endpoints (e.g. respiratory, renal) (98). These endpoints are not considered relevant for the occupational exposure situation and are mentioned here very briefly or not at all. Some studies concerning other effects more relevant for the risk assessment of PCBs are described below. Mostly, low-dose studies and the most sensitive species have been selected, although especially for single congeners, some high-dose studies are described to facilitate comparison. The subhuman primates and guinea pigs are generally more sensitive to PCBs than dogs, rats, mice and rabbits (207). Dermal/ocular, immunological and neurobehavioral changes are particularly sensitive indicators of toxicity in monkeys exposed either as adults or during pre- and/or postnatal periods (19).

The dioxin-like PCBs are generally considered to be the most toxic PCB congeners, although the potency differs considerably between different dioxin-like PCBs and the amounts present in commercial PCB mixtures are small compared to the amounts of non-dioxin-like congeners (98, 188, 402). For PCB 126, the most potent of the dioxin-like PCBs, increased incidences of non-neoplastic lesions (in liver, lung, thyroid gland, spleen, thymus, pancreas, heart, adrenal cortex, kidney, clitoral gland and mesenteric artery) as well as neoplastic lesions were seen in female rats at dose levels ≤ 1 µg/kg bw/day at long-term peroral administration. Body weights were decreased at doses ≥ 0.175 µg/kg bw. Significantly increased incidences of toxic hepatopathy as well as bronchiolar metaplasia of alveolar epithelium were seen at dose levels ≥ 0.03 µg/kg bw. Liver weights and activity of enzymes, e.g. EROD, in the liver and the lung were significantly increased at dose levels as low as 0.01 µg/kg bw (280) (see also Sections 10.2.2–10.2.4 and 10.4).

10.1 Effects of single exposure

The acute toxicity of Aroclors after a single oral exposure is generally low in rats (187). The lethal dose for 50 % of the exposed animals at single administration (LD_{50}) has been reported to be 4 250, 1 010–1 295 and 1 315 mg/kg bw for Aroclors 1242, 1254 and 1260, respectively (188). The time to death is short, less than three days (2). Clinical signs in rats include diarrhoea, respiratory depression, dehydration, decreased response to pain stimuli, unusual gait, oliguria and coma. Histopathological changes (vacuolar degeneration, fatty infiltration) in liver and kidney have been seen after a single high dose of a PCB mixture. Further, patho-

logical findings like haemorrhagic lung, stomach and pancreas have been reported (188). Monkeys sacrificed 4 days after gastric intubation of Aroclor 1248 at 1 500 or 3 000 mg/kg bw exhibited enlarged livers with proliferation of the endoplasmic reticulum and hypertrophy and hyperplasia of the gastric mucosa (187). At dermal administration to rabbits, LD_{50}s were 794–1 269 mg/kg bw for Aroclors 1242 and 1248, 1 260–3 169 mg/kg for Aroclors 1221 and 1262, and 1 260–2 000 mg/kg for Aroclors 1232 and 1260 (19).

Only a few LD_{50}s for individual congeners have been reported. Values between 1 800 and 5 800 mg/kg bw for PCBs 31, 52, 101, 149 and 183 were reported for NMRI mice at peroral administration, whereas the LD_{50} for PCB 153 was 1 000 mg/kg bw. Much lower LD_{50}s have been reported for non-*ortho* PCBs. Oral LD_{50}s for PCB 77 and PCB 169 in guinea pigs were reported as < 1 and 0.5 mg/kg bw (2). For TCDD, the acute toxicity varies over 5 000-fold between animal species at oral administration, with guinea pigs as the most sensitive species (oral LD_{50} 0.001 mg/kg bw) (2, 280).

10.2 Effects of repeated exposure

10.2.1 Dermal and ocular effects

PCB-related dermal and ocular effects are well characterised in monkeys after long-term oral exposure to commercial PCB mixtures. PCDFs may have contributed at least to some of these effects (19). Ocular effects and changes to finger-/toenails and nailbeds were reported as the most sensitive clinical responses in adult rhesus monkeys to daily ingestion of Aroclor 1254 for several months (15).

Nail changes were reported in female rhesus monkeys at treatment with 5 µg/kg bw/day of commercial Aroclor 1254 over a 37-month period, although the same authors reported that nail and nailbed changes were seen in monkeys receiving 40 or 80 µg/kg bw/day over a 72-month period (not mentioned for the 5- and 20-µg/kg bw/day groups) (15, 16, 19). In addition, dose-related ocular effects including eye exudate and prominence of the tarsal (Meibomian) glands were reported and enlargement and/or inflammation of the tarsal glands were stated to occur at the lowest dose level (5 µg/kg bw/day). This dose level corresponded to mean blood PCB levels around 10 µg/l (determined at 19–27 and 55 months of PCB exposure) (15, 19, 386, 387). At peroral treatment of rhesus monkeys with 200 µg/kg bw/day of Aroclor 1254 for up to 28 months, the prominent clinical findings included Meibomian gland enlargement, blepharitis, loss of eyelashes, periorbital and facial oedema, finger nail detachment, and gingival hyperplasia and necrosis of varying severity (19, 388).

Dermal and ocular signs of toxicity including acne, alopecia, erythema and swelling of the eyelids were seen to some degree after 2–6 months in rhesus monkeys at peroral administration of approximately 100 µg/kg bw/day of Aroclor 1248 (19, 26).

Facial oedema and reddening of the eyelids were reported when rhesus monkeys were exposed perorally to estimated doses of 120 µg/kg bw/day of Aroclor 1242 for 2 months (19).

In a study on cynomolgus monkeys, dermal signs were seen in a monkey given a PCB mixture containing PCDFs (2 mg PCB/kg bw/day + 8 µg PCDFs/kg bw/day) in the diet for 20 weeks but were not observed in a monkey given the PCB mixture with PCDFs removed (215).

Treatment of rats for 90 days with several PCB congeners in the diet, both dioxin-like and non-dioxin-like, did not result in any treatment-related histological alterations in the eye or optic nerve. Doses ranged from 9 µg/kg bw/day for the dioxin-like PCB 126 to approximately 4 mg/kg/day for some mono- and di-*ortho*-substituted congeners (19).

10.2.2 Immunological and haematological effects

Immunological effects of PCBs include morphological changes in organs related to the immune system, e.g. thymus, spleen and lymph nodes, as well as functional impairment of humoral and cell-mediated immune responses (19, 98, 188). No cross-species generalisations can be made regarding effects on the thymus, spleen and lymph nodes (188). Immunological effects occur in all species examined at high doses, and in some species, such as the monkey, at low dose levels (188). In general, data indicate that the dioxin-like congeners are more potent than the non-dioxin-like congeners and that higher chlorinated Aroclors are more immunotoxic than lower chlorinated Aroclors (166). Thymic atrophy is one of the hallmark immunotoxic responses to dioxin-like compounds (280). Antibody production against sheep red blood cells has been suggested as a sensitive endpoint for assessing PCB effects, which can be seen as decreased IgG and IgM levels (188).

In early studies, decreased antibody responses to sheep red blood cells, increased susceptibility to bacterial infections and/or histopathological changes in the thymus, spleen and lymph nodes were found in adult monkeys and their offspring at oral administration of Aroclor 1254 or 1248 at 100–200 µg/kg bw/day doses. However, these findings are limited by small numbers of animals and dose levels (19).

A more extensive characterisation of immunological effects in non-human primates was done in later studies. It involved assessments on groups of 16 female rhesus monkeys performed after 23 and 55 months of oral exposure to 5, 20, 40 or 80 µg/kg bw/day of Aroclor 1254 (in a gelatine capsule). The mean levels in whole blood at 19–27 months were around 10, 34, 75 and 112 µg/l, respectively. At 55 months, the corresponding mean levels were 10, 40, 60 and 124 µg/l. The immune parameters that were most consistently affected in the monkeys were IgM and IgG antibody responses to sheep red blood cells. Significant dose-related decreases were seen at a level as low as 5 µg/kg bw/day. The data suggest that the effects of Aroclor 1254 at the investigated dose levels may be due to altered T-lymphocyte and/or macrophage function. The B-lymphocytes did not appear to be the primary target since antibody synthesis to pneumococcal vaccine was not supressed (19, 188, 386, 387). Analytical laboratory data during the prebreeding phase for rhesus monkeys given 5, 20, 40 or 80 µg/kg bw/day of Aroclor 1254 demonstrated a linear decrease in mean platelet volume levels over time for the 3 higher dose groups. The overall levels were significantly lower at 20 and 80 µg/kg bw. Further, a linear decrease over time for red blood cell count was reported for monkeys in the two highest dose groups and the overall level was significantly lower ($p < 0.05$)

at 80 μg/kg bw. In addition, significantly lower ($p < 0.05$) overall haematocrit and haemoglobin concentrations were seen at 80 μg/kg bw (12).

Thymic atrophy was reported in adolescent male rats exposed to Aroclor 1242 in the diet or by inhalation (33 μg/kg bw/day in food or whole body exposure to 0.9 $\mu g/m^3$, 23 hours/day) for 30 days. It was calculated that the rats were inhaling an average of 0.46 μg PCB/kg bw/day (assuming complete absorption), but dermal and oral uptake may have contributed to absorption, yielding a higher total dose (59).

In a recent inhalation study, no significant effects on measured immune parameters were reported in rats repeatedly exposed to high levels of PCB vapour. Analysis of bronchoalveolar lavage (BAL) fluid showed no significant changes in total and differential cell counts (macrophages, neutrophils, lymphocytes), levels of total protein, lactate dehydrogenase activity or cytokine (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, interferon-γ, tumour necrosis factor alpha (TNFα)) levels. Histological evaluation of the upper respiratory tract and lung showed unremarkable or minimal changes that were not considered treatment-related, but no further details were reported. The rats were exposed nose-only for 2 hours/day (two 1-hour exposures separated by a 2 hour break) for 4 ($n = 2$) or 10 days ($n = 7$) to 8 200 $\mu g/m^3$ of a vapour PCB mixture generated from Aroclor 1242 and consisting mainly (ca 90 %) of mono-, di- and trichlorobiphenyls. Assuming an uptake of 80 % (indicated from acute exposure data, see Section 7.1) and a body weight of 200 g, the inhaled amount would correspond to approximately 560 μg PCBs/kg bw/day (180).

A series of toxicity studies was performed on rats, which were exposed to diets containing four dose levels of various single congeners for 13 weeks. Endpoints relevant to the immune system included total and differential white blood cell counts, spleen weight, and histology of the spleen, thymus, mesenteric lymph nodes and bone marrow. Thymic changes (reductions in cortical and medullary volume, atrophy) and to a lesser extent changes in the bone marrow were observed at exposure to PCB 126 (about 0.8 μg/kg bw/day). Reduced cortical and medullary volume and thymic weight were seen following treatment with PCB 105 (males/females: 4.3/4 mg/kg bw/day), whereas mild morphological changes in the thymus were found after treatment with PCB 28 (males/females: 3.8/4 mg/kg bw/day) and PCB 153 (males/females: 3.5/4.1 mg/kg bw/day). No effects relevant to the immune system were reported following exposure to PCB 77 (males/females: doses up to 0.77/0.89 mg/kg bw/day), PCB 118 (males/females: doses up to 0.68/0.17 mg/kg bw/day) or PCB 128 (males/females: doses up to 4.2/4.4 mg/kg bw/day) (19, 65-69, 227).

In a National Toxicology Program (NTP) study, the incidence of thymic atrophy was significantly elevated after administration of PCB 126 by gavage to female rats at daily doses ≥ 0.55 μg/kg bw for 31 weeks or ≥ 0.175 μg/kg bw for two years. Atrophy of lymphoid follicle in the spleen was seen at 1 μg PCB 126/kg bw for two years (280). In a similar study with PCB 153 (doses up to 3 mg/kg bw/day), a significantly increased incidence of bone marrow hyperplasia was recorded at administration for two years at the highest dose level (279).

In vitro phagocytosis was evaluated on human neutrophils and monocytes with PCBs 138, 153, 169 and 180 in equal concentrations (5–25 ppm). The three individual non-coplanar PCBs significantly reduced both neutrophil and monocyte phagocytosis, compared to the unexposed control. PCB 169 significantly reduced monocyte (but not neutrophil) phagocytosis, but to a lesser extent than the non-coplanar PCBs. Neutrophil viability, but not monocyte viability, was decreased for the three non-coplanar PCBs (236).

PCBs 28 and 52 caused rapid cell death among rat thymocytes *in vitro*, whereas PCB 77 did not cause this effect at the same exposure concentration. PCB 52 induced apoptosis in mice spleen cells *in vitro*, in contrast to some dioxin-like PCBs (132).

10.2.3 Hepatic effects

Hepatotoxicity is a well-documented effect in animals exposed to commercial mixtures or single congeners of PCBs. The spectrum of possible hepatic effects in animals includes microsomal enzyme induction, liver enlargement, increased serum levels of liver enzymes and lipids, altered porphyrin and vitamin A metabolism, and histologic alterations that progress to fatty and necrotic lesions and/or tumours. Mild liver effects seem to be reversible (19). Hepatic enzyme induction and liver pathology occur in all species studied, although with differing susceptibility (2). A gradation between different groups of PCBs for liver effects (histology) in animals has been reported, although there are deviations; non-*ortho* > mono-*ortho* > di-*ortho* > others (28).

Induction of microsomal enzymes appears to be one of the most sensitive hepatic alterations produced by PCB mixtures in laboratory animals and was seen in rats fed 30 µg/kg bw/day (lowest dose tested) of Aroclors 1242, 1248, 1254 or 1260 for 4 weeks. Further, hepatic microsomal enzyme activities, liver weight and lipid deposition in the liver were increased in rats fed 250 µg/kg bw/day Aroclor 1242 for 2 months (19, 98, 245).

No histological changes were seen in the liver of adolescent male rats following whole-body exposure to 0.9 µg/m^3 Aroclor 1242 vapour 23 hours/day for 30 days or after exposure to 33 µg/kg bw/day in the diet for 30 days. It was calculated that the rats were inhaling an average of 0.46 µg PCBs/kg bw/day (assuming complete absorption), but dermal and oral uptake may have contributed to absorption, yielding a higher total dose (59).

Further, no treatment-related changes in the liver (histologic evaluation) were stated to occur (no details reported) in rats exposed to high PCB levels. The rats were exposed nose-only to 8 200 µg/m^3 of a vapour PCB mixture generated from Aroclor 1242 consisting mainly (ca 90 %) of mono-, di- and trichlorobiphenyls. The animals were exposed in total for 2 hours/day (two 1-hour exposures separated by a 2-hour break) for 4 (n = 2) or 10 days (n = 7). Assuming an uptake of 80 % (indicated from acute exposure data, see Section 7.1) and a body weight of 200 g, the inhaled amount would correspond to approximately 560 µg PCBs/kg bw/day (180).

Intermediate and chronic duration oral studies indicate that monkeys are more sensitive than rats and other laboratory species to the hepatotoxic effects of PCBs

(19). When given in the diet to rhesus monkeys, approximately 100 and 200 µg/kg bw/day of Aroclor 1248 induced significantly higher serum glutamic pyruvic transaminase activities and significantly lower albumin/globulin ratios in serum, as compared to controls at month 8. One monkey from each group died after administration for 173 days (low-dose group) and 370 days (high-dose group), respectively. These animals showed e.g. lipid accumulation and focal areas of necrosis in the liver (19, 26). Exposure to Aroclor 1254 caused liver enlargement, fatty degeneration, hepatocellular necrosis, and hypertrophic and hyperplastic changes in the bile duct in rhesus monkeys fed 200 µg/kg bw/day for 12–28 months (19).

Rhesus monkeys that ingested capsules containing 5, 20, 40 or 80 µg/kg bw/day Aroclor 1254 for 72 months had a dose-related increase in relative liver weights. The average liver weight for the monkeys in the 80 µg/kg bw/day group was approximately 50 % larger than that in the control group and was attributed to hyperplasia. Also e.g. decreased serum levels of total bilirubin (80 µg/kg bw/day, $p < 0.05$) and cholesterol (40 and 80 µg/kg bw/day, $p < 0.05$) with significant linear dose-related trends were reported. A comprehensive analysis of plasma lipids/lipoproteins after 37 months revealed that plasma triglycerides were significantly elevated at all doses tested except 40 µg/kg bw/day. Suppression of total cholesterol became significant at 40 µg/kg bw/day and high-density lipoprotein cholesterol decreased significantly at 80 µg/kg bw/day. The concentration of PCBs in the blood of monkeys given 5, 20, 40 or 80 µg/kg bw/day Aroclor 1254 increased in a dose-related manner during the first 10 months of dosing, from an average predosing level of 2.3 µg/l to an average of 10, 32, 68 and 105 µg/l, respectively. After 25 months of dosing when approximately 90 % of the monkeys had attained a steady state, the average concentrations were 10, 37, 72 and 118 µg/l, respectively (12, 16, 19, 29, 98).

In studies of single congeners, subchronic toxicity was investigated in rats following dietary exposure for 13 weeks. Hepatic effects included increased liver weight, biochemical changes and histopathology. The most toxic congener was PCB 126 with a lowest observed adverse effect level (LOAEL) of about 0.8 µg/kg bw/day, which was approximately 1/50 of the LOAEL of around 40 µg/kg bw/day for PCB 105 (19, 65, 67). The no observed adverse effect levels (NOAELs) for effects on liver for PCBs 28, 128 and 153 were judged to be in the range of 30–40 µg/kg bw/day, whereas the corresponding LOAELs were 10 times higher. Significantly increased liver EROD activities (expression of dioxin-like activity) were reported at the highest dose levels for PCBs 28 and 128, i.e. about 4 mg/kg bw/day, and at ≥ 4 µg/kg bw/day for PCB 153. EFSA estimated body burdens at the NOAELs (from the reported accumulated concentrations in the fat tissue) of 0.4, 0.8 and 1.2 mg/kg bw for PCBs 28, 128 and 153, respectively (68, 69, 98, 227). Considering dose-response and severity of liver effects, the order of toxicity according to ATSDR was as follows: PCB 126 > PCB 105 > PCB 118 > PCB 77 > PCB 153 > PCB 28 > PCB 128 (19). However, in one 13-week study in rats, PCB 128 was estimated to be equally hepatotoxic as PCB 153 (362). Still, minor contamination of dioxin-like compounds may have been present (and sufficient)

to explain the effects seen at administration of the non-dioxin-like PCB congeners (98).

The liver was shown as a primary target tissue in an NTP study on female rats administered 0.01, 0.03, 0.1, 0.175, 0.3, 0.55 and 1 µg PCB 126/kg bw by gavage for 5 days/week for up to two years (280). Hepatic EROD and pentoxyresorufin-*O*-deethylase (PROD) activities were significantly increased at all dose levels and acetanilide-4-hydroxylase at doses ≥ 0.03 µg/kg bw at all interim evaluations (14, 31, 53 weeks). Absolute and relative liver weights were significantly increased in all dosed groups at 14 and 31 weeks and in all groups administered ≥ 0.175 µg/kg bw at 53 weeks. Hepatic cell proliferation data showed significant increases at doses ≥ 0.175 µg/kg bw at 14 and/or 31 weeks but not at 53 weeks. Increased incidences of hepatocyte hypertrophy were seen after 31 weeks (minimal to mild changes) and 2 years of administration at doses ≥ 0.03 µg/kg bw, and increased in severity at the two highest dose levels with time. A number of other dose-related non-neoplastic liver lesions were found at 53 weeks and 2 years, e.g. inflammation, diffuse fatty change and oval cell hyperplasia at ≥ 0.1 µg/kg bw (2 years) and bile duct hyperplasia at ≥ 0.175 µg/kg bw (2 years). Significantly increased and dose-related incidences of toxic hepatopathy were seen at ≥ 0.03 µg/kg bw (the degree increased with dose) (280). For neoplastic lesions of the liver, see Section 10.4.

In a similar 2-year study of PCB 153 (purity > 99 %), groups of female rats received 0, 0.01, 0.1, 0.3, 1 or 3 mg/kg bw/day by gavage for up to 105 weeks. EROD activity in the liver was significantly elevated at all dose levels at week 31 but not at week 53 (this may indicate some dioxin-like contamination). Significant elevations were also seen for acetanilide-4-hydroxylase (week 31) and pentoxyresorufin-*O*-deethylase (weeks 14, 31, 53) at doses ≥ 0.1 mg/kg bw. Absolute and relative liver weights were significantly greater in rats administered ≥ 0.1mg/kg bw at week 53. The incidences of hepatocyte hypertrophy were significantly increased at doses ≥ 0.3 mg/kg bw at 31 and 53 weeks and in all dosed groups at 2 years, although the grade of lesion was minimal to rather mild. Further, at two years, diffuse fatty changes in the liver and bile duct hyperplasia were increased at doses ≥ 0.3 mg/kg bw and the incidence of oval cell hyperplasia of the liver significantly increased at 3 mg/kg bw (all these changes were rather slight). Toxic hepatopathy was not indicated in this study (279).

CYP1A gene expression was studied in cultures of hepatocytes from human donors, rats and rhesus monkeys, and in human hepatoma cells at exposure to PCB 126 and Aroclor 1254. There were large species differences and human was the least sensitive species. For example, the half maximal effective concentration (EC_{50}) for induction of CYP1A enzyme activity (EROD) was 2.2×10^{-10} M and 3.3×10^{-10} M for monkey and rat cells, respectively, and 1.5×10^{-7} M/4.5×10^{-8} M for human cells (hepatoma cells/hepatocytes) for PCB 126. Corresponding EC_{50}s for Aroclor 1254 were 1.5×10^{-7} M (monkey cells), $\geq 2.7 \times 10^{-6}$ M (rat cells) and $> 3.0 \times 10^{-4}$ M/$\geq 4.8 \times 10^{-5}$ M for human cells (hepatoma cells/hepatocytes) (359).

10.2.4 Endocrine effects and effects on the retinoid system

Studies in animals including rodents and non-human primates provide strong evidence of thyroid hormone involvement in PCB toxicity. Depending on dose and

duration, PCBs can disrupt the production and disposition of thyroid hormones at a variety of levels, and in some studies, histological changes in the thyroid gland were seen (19).

In chronic-duration studies, enlarged thyroid glands and follicles with desquamated cells were observed in rhesus monkeys exposed to 200 µg/kg bw/day Aroclor 1254 for 28 months, whereas treatment with the same dose for 12 months did not induce histological alterations in the thyroid in cynomolgus monkeys (19). Further, no treatment-related alterations on thyroid tissue were shown in rhesus monkeys receiving doses of 5, 20, 40 or 80 µg/kg bw/day Aroclor 1254 for 72 months at histopathological examination. Also, no significant differences between treatment groups for T_4, % T_3 uptake and free T_4 index were indicated and there was no evidence of a linear dose-related trend (16).

Various effects on the thyroid gland and thyroid hormone system have been observed in rats exposed to Aroclor 1254. Total concentrations of T_4 and T_3 in serum were depressed at administration of approximately 90 µg/kg bw/day in the diet for 5 months. At this dose level, a significant depression of the serum level of total T_4 was reported on day 35 compared to the control and pre-treatment levels (19, 54). In another study, serum levels of T_4 decreased when weanling rats received daily gavage dosages of 100 µg/kg bw/day Aroclor 1254 for 15 weeks (141). On the contrary, adolescent male rats exposed to Aroclor 1242 (33 µg/kg bw/day in food or whole body exposure to 0.9 µg/m^3, 23 hours/day) for 30 days had higher serum concentrations of total T_3 and total T_4 than rats in a control group (especially following inhalation exposure). In the rats exposed to the aerosol, histological changes typical of thyroid-stimulating hormone (TSH) stimulation were seen as well. It was calculated that the rats were inhaling an average of 0.46 µg PCB/kg bw/day (assuming complete absorption), but dermal and oral uptake may have contributed to absorption, yielding a higher total dose (59).

Also, histopathological lesions of the thyroid gland developed in male and female rats at exposure to single PCB congeners in food for 13 weeks. These changes were evident to varying degrees of severity for PCB 126 (~ 0.8 µg/kg bw/day), PCB 105 (~ 40 µg/kg bw/day), PCB 77 (~ 80 µg/kg bw/day), PCB 118 (males/females: 70/170 µg/kg bw/day), PCB 28 (~ 360 µg/kg bw/day), PCB 128 (~ 430 µg/kg bw/day) and PCB 153 (males/females: 346/428 µg/kg bw/day) (65-69, 227). The NOAELs for effects on thyroid of the non-dioxin-like PCBs 28, 128 and 153 were 30–40 µg/kg bw/day. EFSA estimated body burdens at the NOAELs (from the reported accumulated concentrations in the fat tissue) of 0.4, 0.8 and 1.2 mg/kg bw for PCBs 28, 128 and 153, respectively (68, 69, 98, 227). However, several PCDDs, PCDFs and apparently PCB 126 are potent thyroid toxicants and, thus, minor contamination might be sufficient to explain (or partly explain) the effects seen at administration of non-dioxin-like PCB congeners (98).

A 2-year NTP gavage study on female rats (0.03, 0.1, 0.175, 0.3, 0.55 and 1 µg/kg bw/day, 5 days/week, and 0.01 µg/kg bw/day for up to 53 weeks only) confirmed alterations in the thyroid hormone homeostasis by PCB 126 (280). Downward trend in serum total and free T_4 concentrations as well as a trend towards increased serum concentrations of total T_3 and TSH with higher PCB 126 concentrations were evident. At the 14-week interim evaluation, significantly decreased

serum concentrations of total and free T_4 were seen at levels ≥ 0.55 µg/kg bw and significantly increased serum concentrations of total T_3 and TSH at ≥ 0.3 and ≥ 0.55 µg/kg bw, respectively. At week 53, total and free T_4 levels were significantly decreased at ≥ 0.175 and ≥ 0.03 µg/kg bw, respectively. Total T_3 levels were significantly increased at ≥ 0.175 µg/kg bw, whereas no significant increase of TSH levels were seen at any dose level. At 14, 31 and 53 weeks, the incidences of follicular cell hypertrophy of the thyroid gland were generally increased in all dosed groups. After administration of PCB 126 for 2 years, these incidences were significantly increased in the 0.3- and 0.55-µg/kg bw dose groups (280).

In a similar 2-year NTP study of PCB 153 (purity > 99 %), groups of female rats received 0, 0.01, 0.1, 0.3, 1 or 3 mg/kg bw/day by gavage, 5 days/week for up to 105 weeks. Significant decreases in thyroid hormone concentrations in serum (week 14: total and free T_4, total T_3; week 53: total and free T_4) were seen at the highest dose level. No significant differences in TSH were seen in any dosed group. At 2 years, incidences of minimal to mild thyroid follicular cell hypertrophy were significantly increased at 0.3 and 3 mg/kg bw/day. An increased liver EROD activity was found at all dose levels at week 31, which may indicate some dioxin-like contamination (279).

Significantly reduced levels of vitamin D_3 metabolites in serum were seen in female rats given 5, 20 or 40 mg/kg diet of a mixture with a PCB pattern resembling that of human breast milk. The mixture was given from 50 days prior to mating and until the offspring was born. The dosages correspond to an average daily intake of about 0.5, 2 or 4 mg PCB/kg bw, respectively, assuming an average body weight of 200 g and a daily diet consumption of 20 g (239).

Hepatic vitamin A levels were dose-dependently reduced both in male and female rats following dietary exposure for 13 weeks to some individual PCBs. The lowest dose at which liver vitamin A was significantly reduced was ~ 0.8 µg/kg bw/day (LOAEL for liver toxicity) for PCB 126, ~ 40 µg/kg bw/day for PCB 105 (LOAEL for liver toxicity), 0.77/0.89 mg/kg bw/day (males/females) for PCB 77, 3.5/4.1 mg/kg bw/day (males/females) for PCB 153 and 4.4 mg/kg bw/day for PCB 128 (females, not observed in males). In contrast, PCB 118 (doses up to 0.68 mg/kg bw/day) had no effects on vitamin A levels in the liver. Other effects on the retinoid system for a few of the congeners included reduction in pulmonary vitamin A and elevated vitamin A levels in the kidneys (65-68, 227). Ulbrich and Stahlmann reported that an oral dose of 10 mg/kg bw/day of Aroclor 1254 reduced hepatic vitamin A levels in mice and rats (396).

10.2.5 Bone effects

Several studies of wildlife suggest that organochlorines including PCBs can impair bone strength and alter bone composition (200, 241, 320). However, there are a limited number of experimental studies showing lesional effects of PCBs on bone tissue.

Andrews reported significant effects on rat femur characteristics including decreased femur length, a narrowing of the femur marrow cavity and a weaker bone in young male rats given Aroclor 1254. The animals were dosed with 0.1, 1, 10 or 25 mg/kg bw/day intragastrically for up to 15 weeks. Femur weight, volume and

length were decreased ($p < 0.01$) at 25 mg/kg bw after 10 and 15 weeks, whereas femur density was increased ($p < 0.01$) at all dose levels at 10 weeks and at the two lowest dose levels at 15 weeks. Significant decreases of other morphometric parameters were found at 10 and 25 mg/kg bw. Bone strength was reduced at 25 mg/kg bw after 15 weeks ($p < 0.05$). Serum calcium levels were elevated ($p < 0.01$) at 5 and 10 weeks (10 and 25 mg/kg bw) but not affected after 15 weeks of exposure. Serum parathyroid hormone, phosphorus, alkaline phosphatase, lactate dehydrogenase and 1,25-dihydroxy vitamin D_3 concentrations were not significantly affected at any dose level or time period. The body weight was reduced ($p < 0.01$) at the highest dose and the relative liver weight significantly increased at the three highest dose levels. Significant elevations of alkaline phosphatase and/or lactate dehydrogenase in urine were seen at all dose levels but were not completely dose-related (9).

Yilmaz *et al* investigated Aroclors 1221 and 1254 (suggested to have oestrogenic and antioestrogenic properties, respectively) following subcutaneous administration of 10 mg/kg bw every other day for a period of 5–6 weeks to intact or ovariectomised rats. Histopathological examination of bone tissue was performed and the level of urinary deoxypyridinoline, a bone resorption marker, and parathyroid hormone, calcitonin, osteocalcin, inorganic phosphate and alkaline phosphatase levels in serum were measured. Administration of Aroclor 1221 led to increased calcium and alkaline phosphatase levels in serum ($p < 0.05$) of intact animals, whereas increased calcium ($p < 0.01$) and inorganic phosphate levels ($p < 0.001$) in serum were seen at administration of Aroclor 1254. In the ovariectomised rats, Aroclor 1221 reduced deoxypyridinoline levels ($p < 0.05$) and increased inorganic phosphate ($p < 0.05$) compared to the ovariectomised control group, whereas Aroclor 1254 raised urinary deoxypyridinoline ($p < 0.01$) and serum parathyroid hormone ($p < 0.001$). Histopathological examination of intact animals indicated that Aroclor 1254 interfered with normal structure of the bone tissue and caused necrosis in some areas and brought about production of hyalinated cartilage. In the ovariectomised animals, these effects were expanded (430).

Effects of Aroclor 1254 on femoral bone metabolism in adult male rats were studied by Ramajayam *et al* (305). The rats were given 2 mg/kg bw intraperitoneally daily for 30 days. Decreased ($p < 0.05$) body weight and absolute weight of femur was seen in the treated animals (this was prevented by simultaneous peroral treatment with vitamin E or vitamin C). Decreased activity of superoxide dismutase, glutathione peroxidase and alkaline phosphatase in femur ($p < 0.05$) and increase in bone tartrate resistant acid phosphatase (TRAP) activity in femur ($p < 0.05$) were also found. In addition, a 5-fold increase ($p < 0.05$) in lipid peroxidation in the femur, measured as malondialdehyde, and a decrease in femoral collagen ($p < 0.05$) compared to control were induced by Aroclor 1254 treatment. Glutathione-*S*-transferase (GST) activity was unaltered. The study suggested that Aroclor 1254 induced oxidative stress, which affected femoral bone metabolism in rats. Further, it was shown that supplementation of vitamin C or vitamin E protected the femur from oxidative stress (305).

Impaired bone strength and altered bone composition were seen in female rats given 5 or 6 doses à 64 µg/kg bw of PCB 126 intraperitoneally for 3 months (total

dose 320–384 µg/kg bw). The treatments also decreased body weight gain and increased relative liver weight (242, 243).

10.2.6 Effects on body weight gain

A decrease in body weight gain was observed in adolescent male rats exposed to 0.9 µg/m^3 Aroclor 1242, 23 hours a day for 30 days. The rate of body weight gain was 33 % as compared to 39 % in controls. It was calculated that the rats were inhaling an average of 0.46 µg PCBs/kg bw/day (assuming complete absorption), but dermal and oral uptake may have contributed to absorption, yielding a higher total dose (59). In a recent study, a significantly lower average body weight gain was observed in rats exposed nose-only 2 hours/day (two 1-hour exposures separated by a 2-hour break) for 4 (n = 2) or 10 days (n = 7) to 8 200 µg/m^3 of a vapour PCB mixture generated from Aroclor 1242 as compared to sham exposed animals. The mixture consisted mainly (ca 90 %) of mono-, di- and trichlorobiphenyls. Assuming an uptake of 80 % (indicated from acute exposure data, Section 7.1) and a body weight of 200 g, the inhaled amount would correspond to approximately 560 µg PCBs/kg bw/day (180).

ATSDR stated that monkeys were particularly sensitive to adverse effects of PCBs on body weight/body weight gain. Effects were seen in monkeys fed Aroclors 1248 and 1242 at dose levels of approximately 100 and 120 µg/kg bw/day, respectively (19, 26).

Additional data on body weight changes appear in other sections.

10.2.7 Neurological effects

Relatively little is known about neurotoxicity and neurobehavioral effects of repeated exposure to PCBs in adult animals although effects following exposure of young animals have been reported in some studies. The most consistent result from studies that examined the neurochemical effects of PCBs is a decrease in dopamine concentrations in different areas of the brain (19).

In a rat study, 52 weeks of exposure by diet to Aroclors 1016, 1242, 1254 or 1260 was not considered to yield any functional or morphological changes indicative of PCB-induced neurotoxicity. The functional observational battery assessed autonomic function, muscle tonus and equilibrium, sensimotor function and central nervous system function. PCB intakes ranged from 1.3 to 14.1 mg/kg bw/day depending on the Aroclor mixture. In the Aroclor 1254 groups, decreased body weight gain was evident late in the study in males receiving approximately 5.8 mg/kg bw/day and in all female dose groups (approximately 1.7, 3.6 and 6.9 mg/kg bw/day) (19).

The exploratory behaviour measured by the open field tests was slowed in adolescent male rats (only males were studied) exposed for 30 days to Aroclor 1242 either by inhalation (whole body exposure) to 0.9 µg/m^3 vapour, 23 hours/day or via diet (0.44 mg/kg) to 33 µg/kg bw/day. It was calculated that the rats were inhaling an average of 0.46 µg PCB/kg bw/day (assuming complete absorption), but dermal and oral uptake may have contributed to absorption (59). In another study, alterations in behaviour including hyperactivity were seen in male rats tested as adults. The rats were fed a diet supplemented with environmental concentrations of

Aroclor 1248 between ages 35 and 65 days (starting around puberty). The mean of the total PCB concentration in adipose tissue was 1.05 µg/g (30).

In monkeys, doses of 0.8–3.2 mg/kg/day Aroclor 1016 in the diet for 20 weeks did not alter the concentrations of noradrenaline, adrenaline or serotonin in the brain. A similar exposure protocol with Aroclor 1016 (predominantly di- to tetrachlorinated PCBs) or 1260 (predominantly hexa- and heptachlorinated congeners) resulted in dose-dependent decreases in dopamine contents in several areas of the brain. Because the concentration of total PCBs was higher in the brains of monkeys treated with Aroclor 1260 than in those treated with Aroclor 1016, the authors suggested that lightly chlorinated congeners were more effective in reducing central dopamine levels than highly chlorinated ones (19).

The lowest doses giving significant decreases in dopamine concentration in some brain areas in 90-day single congener studies in rats were 4.5 µg/kg bw/day for PCB 128 (females: frontal cortex), 37 µg/kg bw/day for PCB 28 (females: substantia nigra), 170 µg/kg bw/day for PCB 118 (females: caudate nucleus, substantia nigra), 428 µg/kg bw/day for PCB 153 (females: frontal cortex) and 4 327 µg/kg bw/day for PCB 105 (males: caudate nucleus) (19, 65, 66, 68, 69, 227).

Shain and co-workers performed an extensive structure-activity relationship study *in vitro*. The PCB congeners were tested in PC12 cells (cell line derived from a pheochromocytoma of the rat adrenal medulla) and the neurotoxic activity was measured as the concentration that reduced the cell dopamine content by 50 % (EC_{50}). Data indicated that *ortho*- and *ortho*-, *para*-chlorine substituted congeners were most potent in reducing cell dopamine content. EC_{50}s < 100 µM (64–97 µM) were seen for PCBs 4, 18, 49, 50, 52, 69 and 104. Congeners without *ortho*-chlorine substitutions (PCBs 2, 3, 13, 14, 15, 39, 77, 126) had little or no effect on the dopamine content. Common indicator congeners like PCBs 101, 118, 138, 153 or 180 were not tested (357).

In another *in vitro* study, the effects of 35 PCBs on the uptake of dopamine into rat brain synaptic vesicles were investigated. The 50 % inhibition concentration (IC_{50}) was used as a measure of neurotoxic activity. IC_{50}s < 10 µM (corresponding to 1.6–3.2 µg/ml) were noted in the most active of the tested congeners (PCBs 41, 51, 91, 103, 112, 118, 143 and 190). PCB 153 had an IC_{50} value of 14 µM (5.1 µg/ml). The PCBs with the lowest activity were PCBs 15, 54, 77, 126, and 169 (IC_{50} > 50 µM, corresponding to > 11–18 µg/ml). Generally the uptake of dopamine into vesicles was inhibited by the *ortho*-chlorinated biphenyls and not by the non-*ortho*-substituted PCBs (260). PCBs 28, 52, 101, 138 and 180 were not tested in the study.

Dopaminergic cells are considered especially vulnerable to ROS, and in a later *in vitro* study by Mariussen *et al*, induction of cell death and ROS formation was investigated. Cultured rat cerebellar granule cells were exposed to PCBs 153 and 126 and to Aroclors 1242 and 1254. PCB 153 and Aroclors 1242 and 1254 induced a concentration-dependent increase in cell death and ROS formation. The concentrations causing 50 % cell death were 8, 30 and 10 µM, respectively, although ROS formation was more efficient with the Aroclors than with PCB 153. PCB 126 had no apparent effects even at 50 µM (261). However, several studies indicate the Ah receptor as having a role in influencing or mediating apoptotic processes.

One study showed that PCB 77 was more efficient than PCB 153 in inducing apoptosis and reducing cell viability in cortical neuronal rat cell cultures at the concentrations used (30–100 μM) (330).

Another *in vitro* study indicated that Aroclor 1254 and the *ortho*-substituted PCB congeners 4, 52, 70, 88, 95, 103, 104 and 153 disrupt Ca^{2+} transport in central neurons by direct interaction with ryanodine receptors in specific regions of the central nervous system. Of the PCBs assayed, PCB 95 exhibited the highest potency. PCBs 4, 52 and 103 and Aroclor 1254 were 2–3 fold less potent than PCB 95 (the other tested congeners were even less potent) and PCBs 66 and 126 were inactive (279, 428).

Based on data from other *in vitro* studies, PCBs 53, 95 and 110 were considered as the most neurotoxic congeners by use of a suggested scheme for assessment of relative neurotoxic potential (361).

10.3 Mutagenicity and genotoxicity

It has been concluded that the overall negative results of *in vitro* and *in vivo* genotoxicity studies indicate that technical PCB mixtures are not directly mutagenic (19, 98). However, there are some indications of involvement of indirect genotoxic mechanisms in the development of PCB-induced cancer (19).

PCB mixtures, e.g. Aroclor 1254, have been found to be generally inactive as mutagens in *S. typhimurium* strains and in several other tests of genotoxicity that may be predictive of tumour initiation capability (19, 98). Aroclor 1254 was shown to induce chromosomal damage and unscheduled DNA synthesis in a few studies *in vitro* (in mammalian/human cells without metabolic activation), but this may be a consequence of high test concentrations. Negative results were obtained when genotoxic effects were investigated *in vivo* in several studies in rats following acute oral exposure to high doses of e.g. Aroclors 1242 and 1254, in two rat studies with intermediate duration oral exposure (about 1–2 months) to Aroclor 1254 and in *Drosophila melanogaster* administered Clophens 30 and 50 (19) (having chlorine contents of 30 and 50 %, respectively) (277). In one study, transient DNA damage in liver cells was seen in rats treated with a high single dose of Aroclor 1254 (19).

In a few studies, binding of highly chlorinated congeners such as PCB 136 and PCB 153 to DNA, e.g. in the liver, has been reported in rodents (98). In a recent study, oxidative DNA damage expressed as accumulation of M_1dG adducts (3-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-pyrimido(1,2-α)-purin-10(3*H*)-one) in the liver was seen in rats exposed for a year to 1 μg/kg bw/day of PCB 126 perorally, whereas no significant effect was seen with PCB 153 at doses of 1 mg/kg bw/day. Co-administration of equal proportions of PCB 153 and PCB 126 resulted in dose-dependent increases in M_1dG adduct accumulation from 0.3 to 1 μg/kg bw/day of PCB 126 and with 0.3–1 mg/kg bw/day of PCB 153. Thus, PCB 153 potentiated the PCB 126-mediated DNA damage. The co-administration of different amounts of PCB 153 with fixed amounts of PCB 126 (0.3 μg/kg bw/day) demonstrated more M_1dG adduct accumulation with higher doses of PCB 153 (196).

Also, experimental evidence supports the hypothesis that lower chlorinated biphenyls are metabolically activated to electrophilic species, which bind to DNA.

The incubation of PCBs 1, 2, 3, 12 and 38 with calf thymus DNA and rat liver microsomes, followed by oxidation with a peroxidase, produced 1–3 major DNA adducts (19, 98). In an *in vitro* study, modified DNA bases formed after bioactivation of PCBs with rat, mouse and human hepatic microsomes were compared in the ^{32}P-postlabelling assay. Eight congeners ranging from mono- to hexachlorinated biphenyls were tested. Modified DNA bases revealed as spots (ROS might be responsible for their formation) were formed with mono-, di- and trichlorinated congeners, but not with higher chlorinated congeners. Higher adduct levels were obtained with the rodent microsomes compared to human microsomes. Using the same technique, low levels of DNA damage were also seen in human hepatocytes exposed to Aroclors 1016 and 1254 (98). Furthermore, it has been shown that PCB-derived monochlorinated phenyl-1,4-benzoquinones can bind to DNA *in vitro* and form specific adducts with guanine bases at the N^2-position (433).

Gene mutations in *S. typhimurium* and unscheduled DNA repair in Chinese hamster ovary cells, indicative of DNA damage, occurred in *in vitro* studies with PCB 3 (98). Further, PCB 3 was shown to induce gene mutations in the livers of transgenic Fisher 344 rats following intraperitoneal injections (600 µmol/ kg, 113 mg/kg bw) once/week for 4 weeks. Both oxidative stress and/or adduct formation could have caused the observed increase in mutations. This study was considered by the authors to be the first to demonstrate the mutagenicity of a PCB *in vivo* (234).

When the mutagenicity of PCB 3 and metabolites was investigated in cultured Chinese hamster V79 cells the results indicated that gene mutations were caused by quinoid metabolites (2′,5′-quinone; 3′,4′-quinone) at non-cytotoxic concentrations. A significant increase in the mutant frequency of the hypoxanthine-guanine phosphoribosyltransferase (*HPRT*) gene was seen by treatment with 0.6–1.3 µM 3′,4′-quinone and 0.5–1.5 µM 2,5′-quinone. The induction of chromosome and genome mutations, detected as micronuclei, was observed only at higher, cytotoxic concentrations of monohydroxylated, catecholic and quinoid metabolites of PCB 3 (432).

Another study investigated effects of the hydroquinones of PCB 1 (2-chloro-2′,5′-dihydroxybiphenyl), PCB 2 (3-chloro-2′,5′-dihydroxybiphenyl) and PCB 3 (4-chloro-2′,5′-dihydroxybiphenyl) and of the catechol of PCB 3 (4-chloro-3′,4′-dihydroxybiphenyl) on Chinese hamster V79 cells. The PCB 2 and PCB 3 hydroquinones very efficiently induced a polyploidisation of V79 cells; the percentage of metaphases with tetraploid chromosome number increased at concentrations $\geq$ 5 µM for both hydroquinones. PCB 2 and PCB 3 hydroquinones produced significant cell death at concentrations $\geq$ 2.5 µM. The PCB 3 catechol caused a significant increase in the sister chromatid exchange frequency at > 5 µM (122).

PCB 52, a tetrachlorinated congener, did not induce gene mutations in *S. typhimurium* with or without metabolic activation (98). Sargent *et al* reported dose-related chromosome breakage in human lymphocytes *in vitro* in a range of non-toxic concentrations of PCB 77 (10^{-1}–10^{-4}µg/ml), but no effect of PCB 52 (332). No increases in micronucleus frequencies or DNA single strand breaks (comet assay) were seen in another *in vitro* study in human lymphocytes treated with PCB 77, whereas DNA single strand breaks were observed following

treatment with PCB 52 in an early *in vitro* study on mammalian cells (98). A recent study indicated that both PCB 52 and PCB 77 caused DNA damage in cultured human lymphocytes in the comet assay and that the non-dioxin-like PCB 52 was at least one order of magnitude more potent than PCB 77 (significant effects at 1 and 10 µM, respectively) (331).

10.4 Carcinogenicity

The carcinogenicity of PCB mixtures has been evaluated in a number of studies in rodents at oral exposure. The studies indicate that commercial PCB mixtures have carcinogenic potential, mainly in the liver, but also to some extent in the thyroid, at doses in excess of those inducing other effects (i.e. in the mg/kg bw range) (19, 98, 185, 186, 279). The International Agency for Research on Cancer (IARC) concluded in 1987 that there was sufficient evidence for carcinogenicity of PCBs in animals. PCBs were classified by IARC without distinction between dioxin-like and non-dioxin-like congeners (98, 186). The dioxin-like PCB 126 is a complete carcinogen in experimental animals and was recently classified by IARC as a human carcinogen (Group 1) based on animal data and mechanistic information (24).

Some tumours (most were benign) were observed in rhesus monkeys perorally dosed with 0, 5, 20, 40 or 80 µg/kg bw/day of Aroclor 1254 for approximately 6 years (16 animals/group). Only one animal in a certain dose group (or in the control group) was affected by a defined type of tumour (with the exception of uterus tumours in one group). However, the total numbers of tumours seemed to be increased in the groups receiving 20–80 µg/kg bw/day. The total numbers of tumours in all groups were 3, 1, 9, 8 and 7 and the number of monkeys with tumours were 3, 1, 7, 7 and 7 (16). Yet, the study was not designed as a cancer study (e.g. some monkeys were necropsied during the study and these data are included as well). It was also stated by the authors that few tumours were seen in the study.

The comparative carcinogenicity of Aroclors 1016, 1242, 1254 and 1260 was examined in Sprague Dawley rats given 50, 100 and 200; 50 and 100; 25, 50 and 100; and 25, 50 and 100 mg/kg diet, respectively, for 2 years. The corresponding mean doses (low to high doses) were 2.0–11.2 (Aroclor 1016), 2.0–5.7 (Aroclor 1242), 1.0–6.1 (Aroclor 1254) and 1.0–5.8 mg/kg bw/day (Aroclor 1260). Aroclor 1254 had the highest dioxin-like activity measured on a TEQ basis. No overt signs of toxicity were seen in any treatment group, although dose-related decreases in body weights were observed, mainly with Aroclor 1254 and especially in females. The liver was the primary target organ in both males and females. Hepatocellular hypertrophy and hepatic foci (foci of cellular alteration sometimes preceding tumours), the principal findings, were observed for all Aroclor treatment groups, although the incidences differed with dose, sex and type of Aroclor. The hepatic tumour response was clearly sex-dependent. For females, a significant and generally dose-related increase in the incidence of hepatic neoplasms was measured for all treatment groups, except the low-dose group of Aroclor 1016. The carcinogenic potency was in the following order: Aroclor 1254 > 1260 = 1242 > 1016. Actually, the tumour incidence differed between the Aroclor mixtures in a manner that

paralleled the differences between Aroclors in total TEQs. For males, a significant response (liver tumours) was observed only for the high dose of Aroclor 1260. Both increases and decreases were seen for non-hepatic tumours. Slight non-dose-related increases in the incidence of thyroid gland follicular cell adenoma s were observed for males receiving Aroclors 1242, 1254 and 1260. For females, a significantly decreased trend in the incidence of neoplastic mammary gland lesions was observed at administration of Aroclors 1242, 1254 or 1260. The morphological appearance of the thyroid tumours was characteristic of those that develop as a secondary response to chronic overstimulation by TSH (264). The presumed mechanism was induction of hepatic enzymes by Aroclor treatment, followed by increased metabolism of T_3 and T_4 and decreased levels in peripheral blood, and as a result enhanced release of TSH from the pituitary gland. This effect is considered as a risk factor in the development of thyroid cancer in rodents, but not in humans. This is based on the fact that the transport of thyroid hormones in the blood follows a different mechanism in humans than in rodents (98, 264).

It was stated by the authors (264), that the results of this comprehensive study clearly indicate that the carcinogenic potency of PCBs is less than was previously assumed. EFSA concluded that the study by Mayes *et al* (264) demonstrated that the total TEQ-doses, associated with dioxin-like constituents within technical mixtures, but not the doses of total PCBs, are mainly, if not exclusively, responsible for the development of liver neoplasms (98). In fact, a comparison with cancer data obtained from chronic exposure of female rats to TCDD showed a very similar dose-response relationship for liver neoplasms (98).

In a later study in rats (49), decreased incidences for females of pituitary tumours (Aroclors 1242, 1254 and 1260), thyroid and skin tumours (Aroclor 1254) as well as adrenal tumours and leukaemia/lymphoma (Aroclor 1242) were reported (in addition to the decrease in mammary tumours). In males, decreased incidences of adrenal, pancreas, prostate and skin tumours were noticed for Aroclors 1242 and 1254. The decreased tumour incidences in males and females were shown at dose levels of 100 mg/kg diet (49), corresponding to approximately 5 mg/kg bw (93).

The NTP has conducted a series of gavage studies in female Harlan Sprague Dawley rats to evaluate the carcinogenicity of some PCB congeners administered alone or as binary mixtures (279-283). PCB 126 (99 % pure), the most potent dioxin-like coplanar PCB, was administered to female rats 5 days/week for up to 2 years at doses of 0, 0.03, 0.1, 0.175, 0.3, 0.55 or 1 µg/kg bw/day. Increased incidences of liver tumours and lung tumours were seen at dose levels ≥ 0.3 and ≥ 0.55 µg/kg bw, respectively. It was concluded that there was clear evidence of carcinogenic activity of PCB 126 based on increased incidences of cholangiocarcinoma of the liver (0/53, 0/55, 1/53, 0/53, 5/53, 6/51, 22/53), squamous neoplasms of the lung (cystic keratinising epithelioma: 0/53, 0/55, 0/53, 0/53, 1/53, 11/51, 35/51; squamous cell carcinoma: 0/53, 0/55, 0/53, 0/53, 0/53, 1/51, 2/51) and gingival squamous cell carcinoma of the oral mucosa (0/53, 1/55, 1/53, 1/53, 2/53, 2/53, 7/53). Hepatocellular adenoma (1/53, 2/55, 1/53, 0/53, 2/53, 4/51, 7/53) and hepatocholangioma (0/53, 0/55, 0/53, 0/53, 0/53, 0/51, 3/53) were also considered to be related to the administration of PCB 126. Equivocal findings were e.g. neoplasms of the adrenal cortex. There were lower incidences of mammary

gland and pituitary gland neoplasms following PCB 126 administration, which was believed to be related to a general endocrine effect as a result of reductions in body weight gain. Body weights were decreased at doses ≥ 0.175 µg/kg bw. Also, increased incidences of non-neoplastic lesions were seen in many tissues, including the liver and lung (280).

Similarly, the non-dioxin-like congener PCB 153 (purity > 99 %) was administered to female rats for up to 2 years at daily doses of 0, 0.01, 0.1, 0.3, 1 or 3 mg/kg bw. The exposure caused non-neoplastic lesions in the liver, although hepatic cell proliferation was not significantly affected at the interim evaluations. Four exposed animals (1 and 3 mg/kg bw groups) developed rare cholangiomas of the liver at 2 years and based on this it was concluded that there was equivocal evidence of carcinogenic activity of PCB 153 in this study. Liver EROD activity was significantly elevated at all dose levels at week 31, but not at week 53, possibly indicating influence of some dioxin-like contamination (279).

When a binary constant ratio mixture of PCB 126 (0, 0.01, 0.1, 0.3 or 1 µg/kg bw) and PCB 153 (0, 0.01, 0.1, 0.3 or 1 mg/kg bw) was administered to female rats for 2 years there were increased and dose-related non-neoplastic effects, e.g. in the liver, lung, oral mucosa, thyroid gland and pancreas, mainly at doses of 0.1 µg/kg bw (PCB 126) plus 0.1 mg/kg bw (PCB 153) and higher. Further, there was clear evidence of carcinogenic activity mainly based on increased incidences of cholangiocarcinoma (0/53, 0/53, 1/52, 9/52, 30/51), hepatocholangioma (0/53, 0/53, 0/52, 2/52, 6/51), hepatocellular adenoma (0/53, 0/53, 3/52, 5/52, 27/51), cystic keratinising epithelioma of the lung (0/53, 0/53, 0/52, 1/53, 11/52) and gingival squamous cell carcinoma of the oral mucosa (0/53, 0/53, 2/53, 5/53, 9/53). Increased incidences of pancreatic acinar neoplasms were also considered to be related to administration of the binary mixture. Furthermore, an effect of increasing the proportion of PCB 153 in the PCB mixture (0.1, 0.3 or 3 mg/kg bw; PCB 126: 0.3 µg/kg bw) was found in several tissues, most notably in the liver. Concerning neoplastic lesions, a significant increase was seen in the incidences of cholangiocarcinoma and of hepatocellular adenoma (281).

In a recent 2-year NTP study, female rats were administered 0, 0.1, 0.22, 0.46, 1 or 4.6 mg/kg bw PCB 118 (purity > 99 %). Clear evidence of carcinogenic activity of PCB 118 was reported based on increased incidences of neoplasms of the liver (cholangiocarcinoma: 0/52, 0/51, 0/52, 0/52, 3/52, 36/49; hepatocholangioma: 0/52, 0/51, 0/52, 0/52, 0/52, 4/49; hepatocellular adenoma: 0/52, 1/51, 1/52, 4/52, 12/52, 24/49) and cystic keratinising epithelioma of the lung (0/51, 0/52, 0/52, 0/52, 0/52, 20/50). Occurrence of carcinoma in the uterus was considered to be related to the administration of PCB 118. The incidences were 2/52, 2/52, 1/52, 3/52, 4/52, 3/52 (11/50 in a group receiving 4.6 mg/kg bw PCB 118 for 30 weeks with no PCB administration thereafter). Equivocal findings were occurrences of squamous cell carcinoma of the uterus and acinar neoplasms of the pancreas (283).

When a binary mixture of PCB 126 (0, 0.062, 0.187, 0.622, 1.866 or 3.11 µg/kg bw) and PCB 118 (0, 0.01, 0.03, 0.1, 0.3 or 0.5 mg/kg bw) was given to female rats in a similar way for 2 years there was clear evidence of carcinogenic activity mainly based on increased incidences of cholangiocarcinoma (0/53, 0/51, 5/53, 19/53, 28/53, 12/65), hepatocellular adenoma (2/53, 1/51, 0/53, 4/53, 17/53, 5/65)

and cystic keratinising epithelioma of the lung (0/53, 0/51, 0/53, 20/53, 49/53, 41/66). The marginally increased occurrence of gingival squamous cell carcinoma of the oral mucosa was also considered to be related to administration of the mixture (282).

It is well documented that orally administered commercial PCB mixtures can promote tumours in the liver and lung of rats and mice following initiation with various genotoxic carcinogens. The commercial PCBs showing promotion in these studies were generally the higher chlorinated mixtures (> 50 % chlorine by weight, e.g. Aroclor 1254) (19, 188). Further, Aroclor 1254 was tested on rat prostate cells *in vitro* and was shown to disrupt gap junctions and expression of connexin 32 and 43, and increase double-stranded DNA breaks, suggesting that PCBs may be able to transform prostate cells leading to carcinogenesis (302).

Single congeners reported to have promoting activity in short-term assays (rat liver) were the dioxin-like PCBs 105, 114, 118 and 126, and some non-dioxin-like di-*ortho*-substituted PCBs (PCBs 47, 49, 153). The non-dioxin-like PCBs 28 and 101 were not found as efficacious tumour promoters in the livers of female rats. The dioxin-like PCBs were generally considered to be more effective than the non-dioxin-like PCBs, although PCB 118 has been reported to be a very weak tumour promoter (19, 98, 216, 404). However, some *in vitro* studies indicated that non-dioxin-like tetra- and hexachlorinated congeners (PCBs 52, 128 and 153) were potent inhibitors of gap junctional cellular communication, an assay that is indicative of tumour promotion capacity (19, 98).

Further, a study by van der Plas *et al* suggested that the majority of the tumour promotion potential of PCB mixtures resides in the non-dioxin-like fraction. Aroclor 1260 was studied in female Sprague Dawley rats and the hepatic tumour promoting activity of a fraction containing the dioxin-like PCBs or the dominating (around 90 % w/w) non-planar 2–4 *ortho* fraction was investigated. After initiation, the animals received a weekly subcutaneous injection of Aroclor 1260 (10 mg/kg bw), a fraction containing all dioxin-like PCBs (1 mg/kg bw; mainly non-*ortho* PCBs, 0.0006 µg TEQs/kg bw), a non-dioxin-like 2–4 *ortho* PCB fraction (1, 3 or 9 mg/kg bw), a combined 0–4 *ortho* PCB fraction (10 mg/kg bw, 0.0006 µg TEQs/kg bw) or PCB 153 (1 or 9 mg/kg bw). Approximately 80 % of the tumour promoting capacity of the 0–4 *ortho* fraction could be explained by the 2–4 *ortho* fraction, while the dioxin-like fraction had only a negligible contribution. Also, it was striking that the 1-mg/kg bw/week 2–4 *ortho* fraction showed a statistically significant effect on the parameter best reflecting the promoting potential, while the same concentration of the dioxin-like fraction did not. Neither was there a significant effect in the low-dose group of PCB 153 (404).

PCBs 52 and 77 and some more low-chlorinated congeners like PCBs 3 and 15 have been suggested to be active in some tests of tumour promotion (rat liver) and to have tumour initiating activity in rat liver (98, 106, 216). Further, the initiating activity of metabolites of PCB 3 was studied *in vivo* in the resistant hepatocyte model and it was shown that two of nine investigated metabolites, 4-hydroxy-PCB 3 and 3,4-benzoquinone-PCB 3, had significantly increased initiating activity (107).

10.5 Reproductive and developmental effects

Toxic effects on fertility and reproductive organs have been observed in a number of studies in animals exposed to PCB mixtures. In rodents, these effects have been seen at rather high or very high oral doses (some mg/kg bw/day or more), whereas minks and monkeys are particularly sensitive to reproductive effects (data on mink are not mentioned here since it is unclear if the mink is an appropriate surrogate to predict human toxicity) (19, 188). Effects reported in female rats include prolonged oestrus, reduced implantation rate and delayed first oestrus in offspring. Effects seen in female monkeys are e.g. prolonged menstruation, decreased fertility and decreased foetal survival (19, 188). In males, high oral doses have induced reductions in sperm counts and impaired fertility in weanling rats, but not in adult rats or mice (19). Effects on gonads and sperms were reported in monkeys at peroral administration of PCB mixtures (3, 6, 19).

PCBs are generally not teratogenic in animals, unless high doses are used. Developmental toxicity as evidenced by e.g. reduced birth weight, and postnatal growth and viability can occur in rodents treated with PCB mixtures in the absence of overt signs of maternal toxicity. The neurobehavioral effects include effects on motor activity, learning and memory, and sexual behaviour (19, 396). Monkeys seem to be much more sensitive to developmental effects of PCBs than rodents and the most sensitive developmental endpoints seem to be those involving neurobehavioural functions. However, in all these studies in monkeys, maternal toxicity was also evident (19, 188).

10.5.1 Effects on fertility

Groups of female rhesus monkeys were exposed to diets containing Aroclor 1248 at levels corresponding to approximately 100 and 200 μg/kg bw/day. Within 4 months, menstrual bleeding and the duration of the menstrual cycle were increased, particularly in the high-dose group. In addition, flattening and prolongation of the serum progesterone peak during the menstrual cycle was observed. After 6–7 months of exposure, the females were mated with control males. Reproductive dysfunction was obvious. There were 8/8 and 6/8 conceptions (the remaining 2 high-dose animals were bred 5 times without success). Resorptions or abortions occurred in 3/8 and 4/6 of low- and high-dose impregnated monkeys, compared to 0/12 in controls, and one of the two infants from the high-dose group was stillborn. Following the total exposure period of about one and a half year, the mothers were put on a control diet. Their menstrual cycles and serum progesterone levels returned to pre-exposure values and their reproductive status showed a recovery. One year after exposure ceased they were mated and 8/8 and 7/7 of the former low- and high-dose females conceived. Abortions or resorptions were observed in 1/8 and 1/7, respectively, and one of the infants of the former high-dose group was stillborn (5, 6, 19, 26).

No irregularities in the menstrual cycles or alterations in serum oestradiol or progesterone were seen in groups of 8 adult female rhesus monkeys fed a diet containing 0.5 or 1.0 ppm of Aroclor 1248, 3 days/week. After being on the experimental diets for 7 months the females were bred to control males. Six out

of 8 animals in the low-dose group and 7/8 animals in the high-dose group gave birth to live infants (6). The dose levels in food would correspond to approximately 6.3 and 13 µg/kg bw/day (43, 336).

Other groups of adult, female rhesus monkeys were fed diets containing Aroclor 1016 equivalent to approximately 7.5 and 30 µg/kg bw/day (stated not to contain PCDFs). The females were mated with untreated males after 7 months of exposure. No maternal toxicity or reproductive dysfunction was seen (27, 187).

Doses of 0, 5, 20, 40 or 80 µg/kg bw/day of Aroclor 1254 (containing 5.2 mg PCDFs/kg) were given perorally in capsules to groups of 16 female rhesus monkeys for up to 72 months (12, 13, 15, 16, 188). No significant exposure-related changes in serum levels of oestrogen and progesterone, menstrual duration or menstrual cycle length or effects on incidences of anovulatory cycles were found during the premating phase (12, 15). After 37 months of exposure, the females were mated with untreated males and dosing was continued throughout mating and gestation. Maternal treatment was discontinued after approximately 7 weeks of lactation, restarted when the infants were weaned at 22 weeks of age and continued for the following 8 months. Incidences for impregnation success were 11/16, 10/16, 4/15, 6/14 and 5/15 in the control to high-dose groups. There was a significant decrease in the conception rate at the three highest dose levels (results at 5 µg/kg bw/day were not statistically significant ($p = 0.085$) after adjusting for the total number of matings). No statistically significant differences in the average gestation lengths across dose groups were seen. At 5 µg/kg bw/day, there were 2 suspected resorptions, 2 stillbirths, 1 abortion and 1 post-partum death. In the three higher dose groups, the number of suspected resorption/abortion/post-partum death (no stillbirths) were 4 (20 µg/kg bw/day), 3 (40 µg/kg bw/day) and 5 (80 µg/kg bw/day), compared to 1 stillbirth and 1 abortion in the control group. The geometric mean concentrations of PCBs in the blood of the dams during the first 8 weeks post-partum (determinations at parturition, 4 and 8 weeks post-partum) were 2, 7 and 30 µg/l in the control, 5 and 40 µg/kg bw/day groups, respectively. The corresponding values in the infants were 10 (controls), 25 and 31 µg/l at parturition, and 2 (controls), 47 and 404 µg/l at 21 weeks post-partum (13, 19). However, blood values differed considerably within groups. Blood values in infants at parturition were 2–66 µg/l (5 animals) in controls and 8–98 µg/l (4 animals) in the low-dose group. Necropsies performed at the end of the post-weaning exposure period showed no exposure-related histopathological changes in the uterus and other parts of the reproductive system or increased incidences or severity of endometriosis (13, 16, 19).

Four adult male rhesus monkeys given Aroclor 1242 in capsules at a dose of 200 µg/kg bw/day for 6 months showed severe structural alterations on gonads and accessory organs and adversely affected spermatogenic activity with few and abnormal sperms. Mean testosterone levels declined during the treatment period, but significantly only in 2/4 animals. The treatment slightly reduced body weights (3).

In a study of four male rhesus monkeys fed approximately 100 µg/kg bw/day of Aroclor 1248 for one and a half year, no effects on sperm morphology and viability or ability to fertilise unexposed females were shown during the first year of exposure. One monkey developed clinical signs of toxicity, decreased libido, a

marked decrease in sperm counts and an absence of mature spermatozoa after the first year of exposure and this animal failed to impregnate females. No such effects were found in the remaining 3 males. However, a biopsy taken one year after removal from the experimental diet showed a complete recovery of spermatogenesis (6, 19).

When adult male rats were injected intraperitoneally with 0.75, 1.5 or 3 mg/kg bw/day of Aroclor 1254 for 20 days, sperm count, motility and daily sperm production were significantly and dose-dependently decreased at the two higher dose levels. These dose levels also caused significant decreases in body weight, testis weight and absolute and relative epididymal weight. Induction of oxidative stress in testicular mitochondria was evident (8).

Fertility in rats was markedly reduced in male offspring exposed to Aroclor 1254 on lactation days 1, 3, 5, 7 and 9 and mated with untreated females 130–150 days post-weaning. Significant decreases in numbers of implants and embryos (21 and 29 % lower than controls, respectively) were observed at 8 mg/kg bw/day, but sperm production, morphology and motility were not affected and plasma follicle-stimulating hormone and testosterone concentrations were not reduced (19, 326).

In contrast, fertility was not impaired in male offspring of rats administered 30 mg/kg/day doses of Aroclors 1221, 1242 or 1260 by gavage on gestation days 12–20, but this study did not include postnatal exposure (19).

No significant treatment effects related to birth weight, litter size, sex ratio, per cent live births or implantation sites were seen when a PCB mixture consisting of 35 % Aroclor 1242, 35 % Aroclor 1248, 15 % Aroclor 1254 and 15 % Aroclor 1260, and with relatively low Ah receptor activity, was given perorally to rat dams from 28 days prior to breading and until weaning at doses of 1 or 3 mg/kg bw/day (296, 324).

In a 2-generation reproduction study, male and female weanling rats were fed diets containing Aroclor 1254 in amounts equivalent to 0.06, 0.32, 1.5, and 7.6 mg/kg bw/day or diets containing Aroclor 1260 in amounts equivalent to 0.39, 1.5 and 7.4 mg/kg bw/day. The F_0 rats were started on the diet at 3–4 weeks of age and the F_1 rats at weaning. Exposure was continuous through mating, gestation and lactation. For Aroclor 1254, a NOAEL of 0.32 mg/kg bw was established based on pup survival and litter size at birth. However, increased relative liver weights were found in F_1 male weanlings at 0.06 mg/kg bw and in all weanlings at $\geq$ 0.32 mg/kg bw. No effect on reproduction was observed with Aroclor 1260, although increased relative liver weights were found in weanlings at all doses tested (244).

Transgenerational effects were investigated in rats (mainly females) following intraperitoneal administration of Aroclor 1221. Dams (F_0) were injected (0.1, 1 or 10 mg/kg bw) on gestational days 16 and 18. The treatments had no significant effect on litter sizes. Litter sex ratio was skewed towards females in the F_1 and F_2 generations (mainly in the 0.1 and 1 mg/kg bw groups), although not significantly when the F_1 and F_2 generations were analysed separately. Compared to controls, serum concentrations of progesterone and luteinising hormone were profoundly altered in F_2 females (significantly lower values in proestrus at all dose levels),

but not significantly altered in F_1 females. No significant effects on postnatal maturational markers (eye opening and markers for timing of puberty) were seen in the F_1 or F_2 generation (372).

Various single congeners were investigated in a series of toxicity studies in which groups of rats were exposed to diets providing four dose levels for 13 weeks. Histological examinations of the female reproductive organs and mammary glands showed mild changes in the ovaries in rats (7/10) exposed to PCB 126 at 8.7 µg/kg bw/day, but not at 0.8 µg/kg bw/day (19, 67). No effects in female reproductive tissues were found at the highest dose level following exposure to PCB 77 (0.9 mg/kg bw/day), PCB 105 (4 mg/kg bw/day), PCB 118 (0.17 mg/kg bw/day), PCB 28 (4 mg/kg bw/day), PCB 128 (4.4 mg/kg bw/day) or PCB 153 (4.1 mg/kg bw/day). Measurements of luteinising hormone and follicle-stimulating hormone in serum, performed only in the female rats exposed to PCB 77 and PCB 28, showed no exposure-related changes (19).

In an NTP-study, however, significantly increased incidences of inflammation in the ovary, oviduct and uterus were seen in rats administered 1 or 3 mg/kg bw/day of PCB 153 (purity > 99 %) for 2 years. Groups of female rats had received 0.01, 0.1, 0.3, 1 or 3 mg/kg bw/day by gavage 5 days/week for up to 105 weeks (279).

No effects in male reproductive tissues were seen in rats at histological examinations following exposure to diets providing 4 dose levels of some single PCB congeners for 13 weeks. The largest administered doses were 0.8 mg/kg bw/day (PCB 77), 4.3 mg/kg bw/day (PCB 105), 0.7 mg/kg bw/day (PCB 118), 7.4 µg/kg bw/day (PCB 126), 3.8 mg/kg bw/day (PCB 28) (4.2 mg/kg bw/day (PCB 128) or 3.5 mg/kg bw/day (PCB 153). Measurements of serum testosterone concentrations, performed only in the male rats exposed to PCBs 28 and 77, showed no exposure-related changes (19).

In mice, some effects were seen following administration in diet of PCB 77 at an estimated dose level of 0.6 mg/kg bw/day. Female mice received PCB 77 for 2 weeks before mating with unexposed males and subsequently throughout gestation and lactation. Female offspring (F_1 generation) were fed the same diets as the dams from weaning until 7 weeks of age, at which time they were mated with unexposed males. Fecundity, litter size, sex ratio and 4- and 21-day survival were recorded. No significant effects were seen at 0.6 mg/kg bw in the F_0 and F_1 females, but all offspring of the F_1 females died before 4 days of age. Further, at the same dose level, the fertilising ability of the eggs *in vitro* was reduced and the egg degeneration rate was increased (only evaluated in F_1 females). No effects were shown in male offspring (F_1 generation) of dams administered dietary doses of 0.6 mg/kg bw/day when the same parameters as in female offspring and sperm motion parameters were recorded (19, 181, 182).

10.5.2 Effects on offspring

10.5.2.1 Effects on weight, growth, viability, signs of toxicity, effects on sexual behaviour: PCB mixtures

Decreased birth weights, a small stature and a decreased body weight gain during nursing were seen in the 6 infants born to female rhesus monkeys exposed to a diet

that provided approximately 100 or 200 µg/kg bw/day of Aroclor 1248 (only one from the high-dose group). Osseous development evaluated radiographically was normal. The infants had areas of hyperpigmentation of the skin at birth, and signs of PCB intoxication (e.g. acne, loss of eye lashes) developed within 2 months. The mothers were exposed before gestation, were maintained on the diets during the gestation and for 3 months following delivery, and had signs of PCB intoxication. Three of the 6 infants died between days 44 and 239. Gross and microscopic examination of the major organs revealed changes in thymus, spleen lymph nodes, bone marrow and liver (5, 6, 19).

One year after receiving a control diet, the females were bred again. The birth weights of the offspring in the former low-dose group (~ 100 µg/kg bw/day) were not significantly different from controls, but signs of PCB intoxication, e.g. mild dermatological lesions and some hyperpigmentation, developed during suckling. 1/7 infants in this group died shortly after weaning and showed signs of PCB toxicity at autopsy. A significant weight deficit of approximately 15 % at birth as compared to controls was reported in offspring conceived 32 months after the end of the maternal exposure to Aroclor 1248 (~ 100 µg/kg bw/day) (6, 235, 336).

Similarly, mild dermatological lesions and hyperpigmentation developed during nursing in rhesus infants, whose mothers were fed Aroclor 1248 in concentrations of 0.5 or 1.0 ppm 3 times/week (corresponding to 6.3 and 13 µg/kg bw/day). Exposure started prior to breeding and continued until after offspring were weaned at 4 months of age. The birth weights were slightly, but not significantly, lower than in controls (6, 43, 336).

Female rhesus monkeys fed a diet that provided approximately 7.5 or 30 µg/kg bw/day Aroclor 1016 were mated after 7 months of exposure and were then further exposed throughout gestation and a 4-month nursing period. Head circumference and crown-to-rump-length of the offspring at birth were not affected by Aroclor 1016, but mean birth weight in the high-dose group was significantly lower than in controls. Both groups of neonates showed some hyperpigmentation (27, 235, 336).

Female rhesus monkeys ingested 0, 5, 20, 40 or 80 µg/kg bw/day of Aroclor 1254 (containing 5.2 mg PCDFs/kg) for 37 months and were then mated with untreated males. Maternal treatment was continued through gestation and was discontinued after 7 weeks of lactation. There were few infants in the different groups due to resorptions, abortions and stillbirths, and most of the infants were females. Mean birth weights were not significantly affected by maternal treatment. Each infant was subjected to anthropometric measurements and clinical examinations until it was 122 weeks old and some data implied smaller head size with increasing PCB dose, but these data were difficult to interpret. Slight clinical signs of PCB intoxication manifested as nail lesions, gum recession and inflammation and/or enlargement of the tarsal glands were seen in the offspring even at the lowest dose level, but were less severe than those of their dams and generally appeared after weaning (nail bed prominence occurred also at birth). Reductions in antibody levels to sheep red blood cells were indicated in offspring of mothers receiving 5 or 40 µg Aroclor 1254/kg bw (no surviving pups in the other dose groups). Immunological testing was initiated when the infants were 20 weeks old and a

notable reduction in IgM titres to sheep red blood cells was found in the low-dose group (5 µg/kg bw). The geometric mean concentration of PCBs in the blood was 7 µg/l in the dams receiving 5 µg/kg bw during the first 8 weeks post-partum and 25 and 47 µg/l, respectively, in the infants of that dose group at parturition and after 21 weeks of nursing. Blood values differed considerably within groups, e.g. blood values in infants were 8–98 µg/l (4 animals) in the low-dose group at parturition (13, 16, 19, 188).

Mild effects on the immune system were noted when groups of rhesus monkeys (3 males, 3 females) and cynomolgus monkeys (10 males) were dosed from birth to 20 weeks of age with 7.5 µg/kg bw/day (a third of the dose given 3 times daily) of a reconstituted PCB mixture (15 PCBs) with a composition analogous to that found in human breast milk. Significant reduction over time in IgM and IgG antibodies to sheep red blood cells (both kind of monkeys) and, for rhesus monkeys, a treatment-related reduction in the level of the human leukocyte antigen (HLA-DR) cell surface marker in peripheral blood leukocytes was found. A significant decrease in absolute mean B lymphocyte numbers was reported for the treated cynomolgus monkeys compared to controls, but the effect was transient, and the authors stated that no significant differences in haematology were found for the cynomolgus monkeys. There were significant increasing trends with time for serum cholesterol and decreasing trends for serum γ-glutamyl transferase and alkaline phosphatase, but no significant differences between exposed and control groups for any of the individual hepatic endpoints were found in the final samples. For the treated rhesus monkeys, there was an increase in platelet number, and trends with time for cholesterol, serum γ-glutamyl transferase and alkaline phosphatase similar to those for cynomolgus monkeys. Clinical findings for cynomolgus monkeys were a slight oedema under the eyes in 5/10 animals. Skeletal development was normal in all infants (determined by X-rays at birth) and no significant differences in birth weights or body weight gains through weaning were observed compared to controls. The weakly dioxin-like PCBs 105, 118, 156, 157 and 189 contributed to almost 1/4 of the mixture. The most common PCBs were PCBs 74, 118, 138, 153 and 180 (almost 3/4 of the mixture). The average PCB levels in blood (14 congeners) at the end of the 20-week dosing period were 2.4 µg/l (range 1.8–2.8 µg/l) in treated cynomolgus monkeys, 1.3 µg/l in similarly treated rhesus monkeys (dosed in liquid diet) and 14.4 µg/l in 3 rhesus monkeys dosed in corn oil, compared to 0.25–0.34 µg/l in controls. The authors concluded that the effects on the immune system possibly were of no biological significance (14).

In mice and rats, anogenital distance is an indicator of prenatal androgenisation (higher androgen level - longer anogenital distance). PCBs have been shown to increase as well as decrease male anogenital distance (396). Increased anogenital distance, especially in the adult period (studied days 3, 21 and 60 after birth), was seen in male offspring of pregnant mice fed 0.05 mg/kg bw/day of Aroclor 1016 during gestation days 16–18. No effect on anogenital distance was seen in female offspring. Also, decreased epididymal weight and increased prostate weight were found and the effect on the prostate was intensified when the offspring reached the adult stage. No effect was found on the testicular weight or size and the treatment did not induce foetal resorption, affect litter size or body weight in offspring. The

androgen receptor binding activity was determined in cellular preparations of the prostate and was permanently increased. It was also shown *in vitro* that Aroclor 1016 induced prostate growth, but did not induce epithelial hyperplasia of the prostate at the doses used (5 and 50 pg/ml) (145).

Significantly increased relative uterine and brain weights on postnatal day 21 were seen in the offspring of rat mothers that had received 4 mg/kg bw/day of a reconstituted PCB mixture simulating the congener content of human milk via food from 50 days prior to mating until birth, but not in the offspring of mothers that had received Aroclor 1254. Increased relative liver weights were seen in pups of both groups. Further, antiandrogenic effects were observed in male offspring in the adult stage. Markedly reduced serum testosterone levels and relative testes weights were shown in both treatment groups. There was also a decreased aromatase activity in the brains of the new-born male pups (significant only in the reconstituted mixture group), and male rats in the reconstituted mixture group exhibited a behavioural feminisation in a sweet preference test as adults, suggesting long-lasting changes in neuronal brain organisation. Aromatase plays a key role in sexual brain differentiation in rodents. No significant changes in number of implantation sites, litter size or sex ratio were found in any of the treatment groups, but the average pup weights (both groups) at birth and during lactation were lower ($p < 0.05$) than in controls. The reconstituted mixture contained PCBs 153 (28 %), 138 (22 %), 180 (14 %), 170 (7.4 %), 118 (7.3 %), 28 (5.9 %), 187 (4.8 %), 156 (3.8 %), 146 (3.1 %), 105 (2.5 %), 101 (1.4 %) and 0.002–0.008 % of PCBs 77, 126 and 169. Aroclor 1254 consists of more than 100 PCB congeners whereby the concentrations of the 14 measured congeners amounted to approximately 50 % of the total PCB concentration (152).

In a later rat study, an identical mixture was given in a similar way at different doses resulting in an average daily intake of 0.5, 2 or 4 mg/kg bw. Significant reductions of serum testosterone concentrations at the highest dose level and a dose-dependent elevation of sweet preference (significant at the highest dose) were found in adult male offspring. In addition, dose-dependent reductions of serum testosterone (significant at the two higher dose levels) and 17-β-oestradiol concentrations (significant at all three levels) were found in weanling female offspring (205). Significantly reduced levels of vitamin D_3 metabolites in serum in female offspring (not investigated in males) were reported in a previous paper at 4 mg/kg bw/day at postnatal day 21 (239). It was stated that the PCB concentrations in adipose tissue from offspring of the low-dose group were approximately 10 times higher than values at the upper margin of current human exposure (205).

In studies by Cocchi *et al* (70) and Colciago *et al* (74), a reconstituted mixture of four PCB congeners (PCBs 138, 153, 180, each representing 1/3 of the total; PCB 126 at a concentration 10^4 times lower) was injected subcutaneously to rat dams from gestation days 15–19 and then twice a week till weaning. It was calculated that this treatment schedule provided an average daily intake of 3.7–4 mg/kg bw. PCB levels in brain were higher in the offspring than in the dams at birth, whereas the opposite was seen in the liver. However, lactation was the major source of exposure in the pups. PCB 126 was not detectable in any of the brain samples (from birth to day 60 postnatally). No signs of gross toxicity in offspring at birth,

or differences in the number of pups per litter, sex ratio or postnatal mortality were seen. A constant reduction of the growth rate was shown in both male and female offspring from weaning to adulthood. Pituitary growth hormone expression and hypothalamic somatostatin expression were altered day 60 postnatally, especially in male offspring. Plasma levels of insulin-like growth factor-1 were higher in PCB exposed rats of both sexes. In adulthood, PCBs caused significant reduction of bone mineral content and cortical bone thickness of tibiae in male rats. Plasma testosterone and thyroid hormone concentrations in males and females were not significantly affected by the exposure. No significant alterations in relative weights of ovary, prostate and testis were observed in offspring and ovarian cyclicity was unaffected. Yet, the results indicated that the PCB exposure produced changes in the dimorphic hypothalamic expression of both aromatase and the 5α-reductases, which were still evident in the adult animals. These enzymes are important for brain masculinisation and differentiation into male and female brains. Female puberty onset occurred earlier than in control animals without cycle irregularity, while testicular descent in males was delayed. A slight but significant impairment of sexual behaviour was also noted in males, whereas the exposure did not seem to affect female sexual behaviour.

The effects of prenatal exposure to the lightly chlorinated PCB mixture Aroclor 1221 on reproductive behaviours were investigated in adult female rat offspring. Rat dams were injected intraperitoneally (0.1, 1 or 10 mg/kg bw) on gestational days 16 and 18 and female-typical sexual behaviours were tested in female offspring, with start postnatal day 50. No significant effects were seen in the low-dose group, when compared to the control group. Overall, the greatest number of effects was seen in the intermediate-dose group. Among the most robust findings in this group was that females vocalised significantly less, (suggestive of a decreased stress response) and required a significantly greater number of mating trials to exhibit receptivity, compared to controls (371).

The effects of gestational (and in some studies lactational) exposures to Aroclor 1254 in rodents on the thyroid gland and thyroid hormone status of foetuses/neonates/pups have been examined in numerous studies. Lesions in the thyroid and depressed serum T_4 and sometimes also T_3 levels were generally seen at rather high dose levels ($\geq$ 1 mg/kg bw/day perorally) (19). However, in one study, depression in both serum total T_4 (not significant) and T_3 concentrations was seen in rat offspring exposed to a lower dose of Aroclor 1254. Dams were dosed with about 0.1 mg/kg bw/day during gestation and lactation, and pups also via diet through postnatal day 30. In addition, significantly decreased choline acetyltransferase activity in hippocampus and basal forebrain was reported at this exposure at 30 days, although there was a significant increase in activity at 15 days of exposure at this dose level (19, 303).

It has been suggested that PCBs might impair hearing due to damage to the outer hair cells of the cochlea via a thyroid hormone dependent mechanism (316). A study with cross-fostering of PCB-treated (6 mg/kg bw/day, perorally) and unexposed litters showed that the critical period for the ototoxicity of developmental Aroclor 1254 exposure was within the first few postnatal weeks in rat, consistent with the greater degree of postnatal hypothyroxinaemia resulting from the greater

magnitude of exposure via lactation (78, 199). Further, the rat cochlea develops postnatally, whereas cochlear tissue in humans develops almost entirely prenatally (78, 135).

In another study in rats, doses of 1, 4 or 8 mg Aroclor 1254 were given via oral gavage from gestation day 6 through postnatal day 21. Body weight deficits were found in the pups in the mid- and high-dose groups and mortalities in these groups were 15 % and 50 %, respectively, at postnatal day 21. Exposure to Aroclor significantly reduced circulating total T_4 concentrations from postnatal day 7 in a dose-dependent manner (all treatment groups, both sexes) compared to controls, but concentrations had returned to near control levels at the age of 30–45 days. The effects on free T_4 in serum were similar. Effects on T_3 were less evident and no significant reductions were found at the lowest dose level. No significant changes in TSH concentrations were seen. Permanent auditory deficits at the frequency of 1 kHz were seen in the adult offspring in the mid- and high-dose group. Auditory thresholds were not significantly affected at higher frequencies (4–40 kHz). Animals from the high-dose group showed reduced auditory startle amplitudes at postnatal day 24 but not when tested as adults (19, 135). A later study by the same authors (167) showed that the developmental exposure of rats to Aroclor 1254 produced a permanent low- to mid-frequency auditory dysfunction and data indicated a LOAEL of 1 mg/kg bw/day. Decreased auditory brainstem response amplitudes at 1 and 4 kHz were seen in all dose groups (same as above) when offspring were tested as adults (167, 199).

Further, significant effects were seen on auditory function in adult rat offspring, whose mothers had been given a PCB mixture consisting of 35 % Aroclor 1242, 35 % Aroclor 1248, 15 % Aroclor 1254 and 15 % Aroclor 1260 (with relatively low Ah receptor activity) perorally from 28 days prior to breading and until weaning, at doses of 1 or 3 mg/kg bw/day. Compared to controls, the groups exposed to the PCB mixture had elevated auditory brainstem response thresholds and distortion product otoacoustic emission (DPOAE) thresholds and attenuated DPOAE amplitudes (the latter significant only at 3 mg/kg bw/day). The effects of PCB exposure were less pronounced in rats exposed to the PCBs in combination with methyl mercury (296). In an earlier, similar study by the same authors, DPOAE amplitudes decreased and DPOAE and auditory brainstem response thresholds were elevated across a range of frequencies at 3 mg/kg bw/day, whereas 1 mg/kg bw/day was the NOAEL (297).

10.5.2.2 Effects on weight, growth, viability, signs of toxicity, effects on sexual behaviour: Single congeners

Reproductive effects were evaluated in the offspring of rat dams given 0.2, 0.6 or 1.8 mg/kg bw of PCB 169 by gavage on day 1 of gestation. Reduced maternal body weight gain, extended mean duration of gestation and reduced mean litter size were seen in the high-dose group. The mating success was reduced and the pregnancy rate dramatically reduced when the F_1 males and females of the high-dose group were paired with treated as well as untreated partners. Preliminary analysis of behavioural records indicated a reduction of specific aspects of sexual behaviour in the treated males (19).

Effects of peroral administration of PCB 118 on gestation day 6 (0.37 mg/kg bw by gavage) were evaluated in male rat offspring. Significant increase in anogenital distance was seen on postnatal days 15 and 21 and prostate and seminal vesicle weights were increased in the adult offspring (relative testis and epididymis weights were reduced). Sperm and spermatid counts were significantly reduced and number of abnormal sperms increased, although levels of luteinising hormone and testosterone were normal. However, when male animals from the same litters were mated with non-exposed females, the numbers of pregnant females, litter size and viable foetuses were not different from control. Increased body and liver weights and decreased relative thymus and spleen weights were also reported in adult male offspring (217). The authors also stated that offspring from the same litters had increased T_4 at puberty (results published elsewhere).

When pregnant rats were given 10 µg/kg bw of PCB 126 or 0.1 mg/kg bw of PCB 77 orally on day 15 of gestation, the birth weights of the pups were reduced (PCB 126) or increased (PCB 77). The age at vaginal opening was delayed in the female pups exposed to PCB 126, whereas no such effect was seen with PCB 77. The anogenital distance was significantly reduced in male progeny and the testosterone concentration decreased in the adult male offspring exposed to PCB 126. Also male sexual behaviour was altered in the offspring, but sperm production was not affected and the pregnancy outcome at mating with untreated females was normal. With PCB 77, the sperm production was increased, an effect that correlated with the increased testicular weight. The testosterone concentration was reduced in the male offspring as adults. No significant effects on pregnancy outcome were seen when the male progeny was mated with untreated females (115).

Effects of PCB 126 on development were studied in rat offspring (mainly in females) of dams orally administrated 0, 1 or 3 µg/kg bw/day from at least 2 weeks prior to mating and until 20 days after delivery. In the high-dose group, 3/7 females failed to become pregnant during the 4-week mating period, but no remarkable changes were observed in the reproductive organs. In offspring, retarded growth was seen in both dosed groups, and histological changes in the ovaries, concomitant reduced ovarian weights and delayed vaginal opening (delay in puberty) in the high-dose group. External urogenital anomalies were shown in both dosed groups in female offspring, but not in male offspring (358).

PCB 77 (0.25 or 1 mg/kg bw) and PCB 47 (1 or 20 mg/kg bw) given intraperitoneally on gestational days 7–18 increased anogenital distance and decreased sexual behaviour as adults in female rat offspring at both doses of PCB 77 and at the high dose of PCB 47. No effects on the sexual behaviour or anogenital distance were found in males. Litter size, sex ratio and survival of the pups were unaffected by the PCB treatments, but the proportion of individuals with eyes open by postnatal day 15 was significantly reduced in males and females in the PCB 77 groups and in the high-dose group of PCB 47. There were no signs of toxicity in the PCB-treated dams or their offspring (407).

Pregnant rats were given a single dose of PCB 132 (1 or 10 mg/kg bw) intraperitoneally on gestational day 15 and effects on parameters related to reproductive organs and sperm function were investigated in adult male offspring. Among the findings in offspring from the 1-mg/kg bw group were significant decreases in

average cauda epididymal weight and epididymal sperm count, and a non-significant decrease in motile epididymal sperm count. Testicular histopathology revealed no differences in spematogenesis compared to controls in any of the groups (179).

No significant differences compared to controls were seen in body weight, organ weights (liver, kidney, testis, prostate, seminal vesicle, ovary), body length or anogenital distance in offspring of rat dams which had received 1 or 4 mg/kg bw/day of PCB 153 orally on gestation days 10–16. Further, no significant changes in the plasma concentrations of T_4, T_3 or TSH were seen in offspring, compared to controls, except a dose-dependent significant ($p < 0.05$) increase in T_3 in 1-week-old males (210).

Developmental toxicity as evidenced by reduced birth weight, reduced serum T_4 and changes in haematology and serum biochemistry parameters was reported in offspring from rats dosed orally with 0.25 or 1 µg/kg/day of PCB 126 beginning 5 weeks before and continuing through gestation and lactation. No significant effect on litter size was observed at 1 µg/kg/day (19).

Subtle signs of toxicity (all exposure groups), increased liver weights and decreased thymus weights (high-dose groups) were seen in offspring of rats exposed perorally to 0.25 or 1 µg/kg bw/day PCB 126 or 2 or 8 mg/kg bw/day PCB 77 during gestation days 10–16. No effects on gestational length, litter size, per cent live births or birth weights were observed (339).

Elevated auditory thresholds for 0.5 and 1 kHz tones were recorded in offspring from rats that received 1 µg/kg bw/day of PCB 126 for 35 days prior to breeding and throughout gestation and lactation. The NOAEL was 0.25 µg/kg bw/day (19, 199).

Peroral administration of 6 mg/kg bw/day of PCB 95 to rats from gestation day 5 to weaning at postnatal day 21 did not result in differences in litter size, sex ratio or weight gain compared to controls. However, abnormal development of the primary auditory cortex was seen, although hearing sensitivity and brainstem auditory responses of pups were normal (206).

Administration of approximately 0.8 or 1 mg/kg of PCB 126 to mice on gestation day 10 significantly increased the percentage of foetuses with cleft palate (19). No foetuses with cleft palate were seen after administration of up to 271 mg PCB 153. Combined administration of PCB 126 and PCB 153 significantly reduced the incidence of cleft palate compared to that produced by PCB 126 alone (19). A dose-related increase in embryotoxicity and in the incidence of malformed foetuses, mainly showing cleft palate and hydronephrosis were found in the offspring of mice administered daily doses of 2, 4, 8 or 16 mg/bw of PCB 169 on days 6–15 of gestation. Dose levels of 0.1 and 1 mg/kg bw were without effects. The authors reported that PCBs 77 and 128 also produced the same teratogenic effects, though they were less potent (187).

10.5.2.3 Behavioural effects (except sexual behaviour): PCB mixtures

Neurobehavioral studies were conducted in the 3 surviving rhesus infants born to mothers fed a diet providing approximately 100 µg/kg bw/day Aroclor 1248 before and during gestation and during lactation. Relative to controls, exposed monkeys

showed hyperlocomotor activity in tests at 6 and 11–12 months of age, which correlated with peak PCB body burdens. Peak PCB body burdens were also correlated with increased errors in 5 of 9 learning tasks conducted between 7 and 24 months of age. The results indicated a deficiency in learning various types of discrimination problems (including spatial and colour discrimination reversal tasks at 7–8 months of age) (42, 43). As young adults, these PCB exposed infants were less active than controls (336).

Hyperlocomotor activity at 12 months of age was also reported in 5 infants delivered by the females after 0.5–1.5 years on a control diet (43). Further, 4 infants conceived approximately 1 year after the end of the maternal treatment with Aroclor 1248 (~ 100 µg/kg bw/day) for one and a half year were tested to investigate discrimination reversal learning at 14 months of age. No significant effects of PCB treatment were seen in those tests. For 3 infants conceived 32 months after the end of maternal exposure to Aroclor 1248, tests at 14 months of age showed that performance was facilitated on the shape problem (336). Tests of the same infant monkeys at 6 years of age (n = 4) or at 4 years of age (n = 3) showed neurobehavioural deficits reflected as impaired performance on a spatial learning and memory task (delayed spatial alternation (DSA), both cohorts combined). It was suggested that these effects were associated with impairments in attentional or associational processes, rather than memory impairment. None of the PCB exposed monkeys exhibited toxic signs at the time of testing (19, 235, 335).

Two groups of breeding mothers (rhesus monkeys) were fed Aroclor 1248 three times/week in concentrations of 0.5 and 1.0 ppm, respectively (approximately 6.3 and 13 µg/kg bw/day). Exposure started prior to breeding and continued until after offspring were weaned at 4 months of age. Five offspring from each group were tested for locomotor activity at 12 months and mean activity levels were higher than in controls, especially for the 0.5 ppm group (43, 336). The offspring of mothers fed 1.0 ppm Aroclor 1248 was tested on discrimination reversal learning at 14 months of age, but no statistically significant effects were seen (336).

Effects on learning and behavioural tasks were also studied in infants of female rhesus monkeys fed a diet providing approximately 7.5 or 30 µg/kg bw/day (7 days/week, 6 infants/group) of Aroclor 1016. The female monkeys were mated after 7 months of exposure and then further exposed throughout gestation and until the offspring were weaned at 4 months of age. Offspring were tested at 14 months of age (discrimination reversal learning) and at 4 years of age (DSA test). Offspring in the high-dose group were significantly impaired in their ability to learn a simple spatial discrimination reversal problem, requiring more than 2.5 times as many trials as matched controls to reach criterion. They required, however, significantly fewer trials than controls to reach criterion on a shape discrimination reversal problem. Fewer trials compared to controls (not significant) were also noticed for offspring in the low-dose group on the shape discrimination reversal problem. Further, a significant decrease was observed in DSA performance in the high-dose group compared to the low-dose group. The performance was impaired in the high-dose group but facilitated in the low-dose group, and none of the two PCB treated groups differed significantly from controls. The authors suggested that the facilitated performance was due to decreased attention paid to weak, peripheral

stimuli which would narrow the focus of attention. By the time of behavioural testing, no toxic health signs related to PCBs were exhibited (235, 335, 336).

Learning and behavioural effects were studied in 8 male cynomolgus monkeys dosed perorally with 7.5 µg/kg bw/day of a mixture of 15 PCBs resembling the composition in human milk, from birth to 20 weeks of age. The dose was divided into three parts and given three times daily for 7 days/week. The PCBs represented 80 % of the congeners typically found in breast milk. The PCBs 74, 118, 138, 153 and 180 contributed to almost 3/4 of the PCBs and the weakly dioxin-like PCBs 105, 118, 156, 157 and 189 to almost 1/4. Behavioural assessment on a series of tasks was performed when the monkeys were 2.5–5 years of age. Robust deficits were observed on DSA, fixed interval, and differential reinforcement of low rate performance. No group differences were observed for the number of errors on a series of non-spatial and spatial discrimination reversal tasks, although there were many more errors by some individuals. The results suggested a learning deficit rather than a deficit in short-term spatial memory *per se*, and were indicative of difficulty in adaptively changing response pattern, e.g. inability to inhibit inappropriate responding, and a less efficient behaviour. Blood and fat levels of PCBs at the end of the dosing period were within the range observed in the general human population. At 20 weeks of age, PCB levels were 1.84–2.84 µg/l in blood and 1 694–3 560 ng/g lipid in adipose tissue (19, 98, 308).

Colciago *et al* administered a reconstituted mixture of four PCB congeners (PCBs 138, 153, 180, each representing 1/3 of the mixture, with traces of PCB 126) subcutaneously to rat dams on gestation days 15–19 and then twice a week till weaning (corresponding to a daily intake of approximately 3.7–4 mg/kg bw). An important alteration in memory retention was seen in male offspring as adults. Two tests performed to evaluate learning and memory gave opposite results. Spatial memory was unaffected by the treatment. Conversely, the passive avoidance test was deeply affected, but only in males. It was indicated that the treatment had impaired the ability to fix in memory an adverse event (74).

No overt signs of maternal toxicity were reported at exposure of rats to a low-chlorinated PCB mixture (Clophen A30, about 0.4 or 2.4 mg/kg bw/day in the diet) that started 60 days prior to mating, extended throughout gestation and lactation in the dams and continued for the offspring after weaning. However, alterations in three activity-dependent behavioural tests were found in adult male offspring (females were not tested) in the high-dose group. These tests were performed 22, 65–75 and 380 days postnatally. No effects were found in the low-dose group. Using a cross-fostering design for examination of sensitive periods for PCB effects, a subsequent study revealed the importance of the prenatal exposure period for these neurobehavioural alterations (19, 188).

Sable *et al* investigated developmental exposure to PCBs and/or methyl mercury and effects on a differential reinforcement of low rates operant task in adult rats of both sexes. PCB exposed male rats showed dose-dependent inhibitory control impairments, but the deficits were not seen when the same PCB doses were given in combination with methyl mercury. The PCB mixture consisted of 35 % Aroclor 1242, 35 % Aroclor 1248, 15 % Aroclor 1254 and 15 % Aroclor 1260 and was found to have relatively low Ah receptor activity. The rat dams were given 1 or 3

mg/kg bw/day perorally, from 28 days prior to breading and until weaning, alone or in combination with methyl mercury (ratios 4.4:1 and 4.9:1) (324).

10.5.2.4 Behavioural effects (except sexual behaviour): Single congeners

It was recently shown that developmental exposure to non-dioxin-like PCB congeners (PCBs 52, 138 or 180) induces different behavioural alterations (in learning or motor coordination) by different mechanisms in rats. Female rats were given PCBs (1 mg/kg bw/day) in food from gestational day 7 to postnatal day 21 and learning, motor coordination and microdialysis experiments were performed when the pups were 3 (males) or 4 (females) months old. The ability to learn a Y maze conditional discrimination task was reduced in rats exposed to PCBs 138 or 180, but not in rats exposed to PCB 52. Also the function of the glutamate-nitric oxide-cGMP pathway (cerebellum) was impaired at exposure to PCBs 138 and 180. In contrast, PCB 52, but not PCBs 138 or 180, increased extracellular GABA in cerebellum and impaired motor coordination (assessed by the rotarod test). The described effects for all three congeners were similar in males and females (37).

In a similar study, female rats were given PCB 153 (1 mg/kg bw/day) or PCB 126 (0.1 µg/kg bw/day) perorally during gestation (from day 7) and lactation (to day 21). Learning tests and microdialysis studies were performed when the pups were 3 or 7–8 months old. The results showed that PCBs 126 and 153 impaired learning ability and glutamate-nitric oxide-cGMP pathway function in cerebellum in young but not in adult (7 months old) rats. In control rats, the function of the glutamate-nitric oxide-cGMP pathway and learning ability were lower in adult than in young rats, whereas these age-related differences were not present in rats exposed to PCBs. All the studied effects were similar in males and females. The authors concluded that the two PCBs can induce similar effects but that the dioxin-like PCB 126 was 10 000-fold more potent than the non-dioxin-like PCB 153. Moreover it was suggested that PCBs may induce neurotoxic effects by mechanisms that are independent of their role as endocrine disrupters, since young male and female rats were affected in a similar manner (293).

Administration every second day on gestational days 10–20 by gastric tube to rats of 2 µg/kg bw of PCB 126 or 1 or 5 mg/kg bw of PCB 118 resulted in impaired discrimination learning and elevated activity levels in a visual discrimination task in male offspring (only males were tested) in the absence of clinical maternotoxic and foetotoxic effects. The effects were most marked in the rats exposed to PCB 126. The offspring was exposed *in utero* but also through mother's milk (175). In a later study, it was concluded that *in utero* exposure to PCB 126 produced more severe neurobehavioural effects in rats than postnatal exposure (2 µg/kg bw every second day from day 3 to 13 after delivery) (177).

In the latter study (177), it was reported that male pups from dams treated similarly (days 3–13 postnatally) with 5 mg/kg bw of PCB 153 had increased motor activity and some attention problems as compared to the controls, but the ability to learn was not seriously affected. Male pups showed a behavioural pattern similar to that observed in spontaneously hypertensive rats, an animal model of attention deficit hyperactivity disorder (ADHD). Female offspring did not exhibit hyperactive behaviour, but had slower acquisition of time discrimination as compared

to the controls, indicating a sex-specific behavioural effect of PCB 153. The exposures did not affect the body weight of the dams or the physical development of the pups. There were low levels of EROD activity in offspring at weaning (176, 177).

At administration via gavage to rats on gestation days 10–16, deficits in spatial learning were observed in female offspring tested as adults at the high-dose levels of PCBs 28 and 153 and at both dose levels of PCB 118. Male offspring were not affected. The mothers had received 8 or 32 mg/kg bw/day of PCB 28, 16 or 64 mg/kg bw/day of PCB 153 and 4 or 16 mg/kg bw/day of PCB 118. No signs of toxicity or effects on gestational weight gains or liver weights were noticed in the dams. When the thyroid hormone status of pups from the litters was evaluated, it was found that only PCBs 118 and 153 reduced serum T_4 concentrations and that serum T_4 were equally depressed in male and female rats (337, 338). In a study with similar exposure of the dams to PCB 95 (8 and 32 mg/kg bw/day), hypoactivity was seen in the offspring as adults (both dose levels) but otherwise no impairments of neurobehavioural function (340). The same authors reported that spatial learning and memory was not impaired in the offspring of rats dosed via gavage to PCB 77 (2 or 8 mg/kg bw/day) or PCB 126 (0.25 or 1 μg/kg bw/day) during gestation days 10–16 (339).

Further, Rice *et al* conducted a series of behavioural studies in offspring from rats dosed perorally with 0.25 or 1 μg/kg bw/day of PCB 126 beginning 5 weeks before and continuing through gestation and lactation. Generally, no significant differences between treated and control rats were seen in neurobehavioural tests (19).

Postnatal reflexes and motor activity were evaluated in male and female rat offspring of dams exposed on gestation day 6 to a single low dose of PCB 118 (0.375 mg/kg bw by gavage). Impairment of postnatal reflexes was found in PCB exposed female offspring. Hyperactivity was seen in both sexes at puberty, although no hyperactivity was noted earlier (days 30–34) (217). The authors stated that offspring from the same litters also had increased T_4 levels at puberty (reported elsewhere).

Exposure to PCB 77 from gestational day 6 through weaning significantly increased dopamine concentrations in the brain in rat offspring at exposure levels ≥ 0.1 mg/kg bw/day. These changes persisted into adulthood (350).

Low-dose co-exposure to PCBs (e.g. PCBs 52, 153 and 126) and other environmental agents like methyl mercury or polybrominated diphenyl ethers during a critical period of the brain's growth and development can interact and increase defective development behaviour and affect learning and memory abilities. Synergistic interaction from co-exposure to PCB 52 and polybrominated diphenyl ether congener 99 on spontaneous behaviour has been indicated. Further, some data suggest that PCB 153 and methyl mercury can act synergistically in the low-dose range, but not in the high-dose range (for further details on this matter, see e.g. references (119, 120). Indeed, some recent studies (139, 365) indicate that methyl mercury may protect against the effects of PCB 153 (and vice versa) on early development, including neurobehavioural functions, in progeny of rat mothers exposed during gestation and lactation.

Altered spontaneous motor activity was seen in 4-month-old male mice given a single gavage dose of 0.41 mg/kg of PCB 77 at 10 days of age (19) (the critical period for exerting effects on brain development in the mouse). When single doses of PCB 28 (0.18, 0.36, 3.6 mg/kg bw), PCB 52 (0.20, 0.41, 4.1 mg/kg bw), PCB 118 (0.23, 0.46, 4.6 mg/kg bw) or PCB 156 (0.25, 0.51, 5.1 mg/kg bw) were given to mice in a similar study, dose-related changes in spontaneous behaviour, significant at the two higher dose levels, were seen in males at exposure to PCBs 28 and 52 (females were not tested). The highest dose of PCB 52 also caused a deficit in learning and memory functions in the adult animal, and affected the cholinergic nicotinic receptors in the cerebral cortex (104). Further, PCB 126 (0.046 or 0.46 mg/kg bw as a single dose) showed effects on the spontaneous behaviour at 2 and 4 months of age at both dose levels. The highest dose also affected learning and memory functions in the adult male mice and in the animals showing this deficit, the cholinergic nicotinic receptors in the hippocampus were affected. No behavioural or neurochemical alterations were seen in mice similarly treated with PCB 105 (0.23, 0.46, 4.6 mg/kg bw) (105). The results for spontaneous behaviour variables indicating an effect in 2- and 4-month-old male mice exposed on postnatal day 10 to an oral single dose of 0.51 mg/kg bw of PCB 153 were given in a recent study (120).

Neurobehavioural studies in which mice were given a single oral dose by gavage at 10 days of age were considered by EFSA. However, the corresponding critical period for exerting effects on brain development in humans is during foetal life in the last trimester and shortly after birth. Thus, EFSA believed that much higher exposure levels would be required to obtain a similar situation in foetal life of humans if assuming a similar kinetics for persistent PCBs in humans. Also, the relevance of high bolus dosing was questioned (98).

11. Observations in man

11.1 Effects of single and repeated exposure

11.1.1 Effects on skin, eyes and mucous membranes

The predominant finding among individuals exposed occupationally to PCBs has been an increased prevalence of abnormal dermatological symptoms (276). During acute exposure, irritative effects such as skin rash, itching and burning sensations have been reported, as well as eye irritation (2). Skin rash or skin irritation in the absence of documented high PCB exposure may be more related to exposure to chlorinated benzenes, organic solvents or other compounds present. Other dermal effects such as temporary inflammation or oedema of the skin and chloracne appear to be related to the incidence and magnitude of the individual's dermal contact with PCB fluids or result from high exposure to heated PCB vapours, suggesting PCBs and/or PCDFs as the causative agents (193). Usually, chloracne appears in individuals with serum PCB levels 10–20 times higher than those of the general population, but there is a great variability among individuals and there may also have been exposure to relatively high levels of PCDFs (19,

209). Chloracne is induced by exposure to dioxin-like substances and PCDFs are relatively potent chloracnegens (19, 193). It has been suggested lately that genetic polymorphisms in *CYP1A1* and *GSTM1* might be related to the susceptibility to PCB/PCDF-induced skin manifestations (389).

Health conditions were evaluated in 80 electric capacitor manufacturing workers in Italy exposed for many years to PCB mixtures (more recently mixtures with 42 % chlorine content). The PCB content in blood samples was expressed as trichlorobiphenyl and pentachlorobiphenyl. Total PCB concentrations were 41–1 319 µg/l in 60 currently exposed workers in two plants. In plant A workers, the mean blood concentration of pentachlorobiphenyls was higher than that of trichlorobiphenyls, while the reverse prevailed in plant B workers. Eight cases of chloracne and/or folliculitis and 5 cases of dermatitis due to primary irritative or allergic sensitising agents were identified. The workers with chloracne were all working in plant A. Their whole blood PCB concentrations ranged from 300 to 500 µg/l but did not differ significantly from the concentrations of 5 unaffected workers on the same job. In workroom air samples, concentrations of trichlorobiphenyls were in the range 48–275 µg/m^3, while significant amounts of pentachlorobiphenyls were often detected on surfaces. Further, considerable amounts of PCBs were detected on the hands of the workers (262, 263).

Among 289 US capacitor manufacturing workers, 40 % reported skin rash to have occurred after initiation of work in the plant. Burning was reported by 26 %. Physical examination revealed that 37 % had dermatological abnormalities, e.g. erythema (14 %), dryness (13 %), hyperpigmentation (10 %) and acne (6 %). Redness of the conjunctiva, palpebral hyperpigmentation and oedema were seen in 17 %, whereas 2 % had abnormal secretions from the eyes and 1 % had enlargement of the Meibomian glands. The exposure to PCB-containing dielectric fluid resulted mainly from inhalation of vapours, but there was also potential for skin contact and ingestion. Mean air levels of PCBs were 7–410 µg/m^3 in some areas but ranged between 900 and 11 000 µg/m^3 in departments where capacitors were immersed in the dielectric fluid. To investigate the association between skin abnormalities and plasma PCB levels, a subgroup of 22 men and 20 women with chloracne, comedones, hyperpigmentation and hyperkeratosis was identified. The male workers with skin abnormalities had higher mean concentrations of higher homologues of PCBs (calculated as Aroclor 1254) in plasma compared to controls (97 vs. 50 µg/l). No significant differences were found for lower homologues of PCBs (calculated as Aroclor 1248) or for women. However, PCDFs should be considered a possible etiologic factor/co-factor. Various mixtures of PCBs (e.g. Aroclors 1254 and 1242) had been used at the facility, but for 5 years prior to the study, Aroclor 1016 and to a minor degree Aroclor 1221 had been used exclusively (118).

In a survey of workers exposed in a plant with production of large power capacitors or at a public utility company with maintenance work on transformers, significant, positive correlations of symptoms suggestive of irritation of mucous membranes, e.g. irritated or burning eyes, were noted with increasing concentration of serum PCBs. A relationship between the incidence of skin rash or dermatitis and plasma levels of higher, but not lower, chlorinated PCBs was also

found. No cases of chloracne were identified. However, potential confounding factors like other irritating compounds were not accounted for. The serum PCB levels were many times higher in the workers than in the general population. Geometric mean serum levels were 502 µg/l (range 210–3 330) of low-chlorinated PCBs (≤ 4 chlorine atoms) and 44 µg/l (range 20–250) of high-chlorinated PCBs (≥ 5 chlorine atoms) for workers in an area of presumed high exposure. Time-weighted average (TWA) personal air sample concentrations of PCBs in some high-exposure areas were up to 264 µg/m^3 (median 81 µg/m^3). Also skin contamination by PCBs was indicated (19, 367).

In a cross-sectional study, 55 transformer repairmen exposed to PCBs from air and contaminated surfaces (predominantly from Aroclor 1260) were compared to 56 subjects never occupationally exposed to PCBs. A thorough skin examination was performed, but no definite case of chloracne was identified. According to questionnaire responses, a number of irritant symptoms (e.g. eye irritation, chest pain on walking, wheezing) were significantly more prevalent in the total group of exposed workers than in the comparison group, although the authors regarded PCBs as relatively non-irritating. However, neither wheezing nor forced expiratory volume for one second (FEV_1) was significantly associated with exposure after adjustment for smoking. Abnormal findings of conjunctivitis or tearing were found in only one exposed worker, indicating that these symptoms were mild and/or transient. A total of 24 personal breathing zone samples (sample duration: 1.0–5.8 hours) were analysed. Sample concentrations of PCBs were ≤ 60 µg/m^3. Eight-hour TWAs of PCBs were 0.01–24 µg/m^3. Further, PCBs were analysed in both serum and lipid tissue, showing at least 2–3 times higher PCB body burdens in the currently exposed subjects than in controls. The PCB patterns resembled Aroclor 1260 (100, 101). The total serum PCB concentrations were, however, substantially underestimated. The total serum values (median and mean) as reported in a later study (27 PCB peaks were quantified) were approximately 43 and 54 µg/l for currently exposed workers, 30 and 39 µg/l for formerly exposed workers and 13 and 20 µg/l for controls (114).

Chloracne and other skin manifestations (e.g. hyperkeratosis), abnormal nails as well as hypersecretion of the Meibomian glands and abnormal pigmentation of the conjunctiva were reported in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs (*Yusho* and *Yu-Cheng* poisoning incidents). The victims were also exposed to PCDFs and other structurally related chemicals and it has been suggested that PCDFs caused most of the health effects seen in the *Yusho* and *Yu-Cheng* patients (2, 19, 389). The median PCB level in serum of about 400 *Yu-Cheng* individuals a few years after the incident was 51 µg/l (389). No adverse dermal or ocular effects have been reported in subjects with high consumption of fish contaminated with PCBs and other environmentally persistent chemicals or in other cohorts from the general population, but it is unknown if these outcomes were systematically studied (19).

11.1.2 Immunological effects

Information on immunological endpoints in PCB exposed workers is scarce, but there are some data on effects in the general population from studies of people

exposed to PCBs e.g. by consumption of contaminated fish and from the *Yusho* and *Yu-Cheng* incidents. These findings include increased susceptibility to respiratory tract infections, decreased total serum IgA and IgM antibody levels and/or changes in T-lymphocyte subsets. ATSDR assessed that the most conclusive findings are those in the *Yusho* and *Yu-Cheng* populations, the populations that experienced the highest levels of PCB exposure, but also exposure to PCDFs. Interpretation of the data from the other human studies was considered complicated because the responses were generally subtle and exposures included a number of persistent toxic substances in addition to PCBs that are also potentially immunotoxic. Thus, conclusions of causality cannot be drawn from these studies (19). In a recent study, PCBs were associated with arthritis in women (231). The results need, however, to be corroborated in other studies.

In a recent prospective and cross-sectional study, there was no evidence of immune system involvement as expressed by a set of cytokines in Swedish workers removing old elastic sealants with PCBs. Male abatement workers (n = 36) with at least 6 months experience of PCB removal in the two previous years (2000–2001) and a control group of 33 matched construction workers without occupational PCB exposure were investigated. Tobacco habits, as well as background exposure to PCBs (e.g. consumption of fatty fish), occupational history and general health were assessed by use of a questionnaire and the result showed that there were more smokers in the exposed group (39 % vs. 9 %). Almost all subjects considered their current work as dusty, but 8 exposed subjects and 27 controls denied using any respiratory protection in dusty work. The cytokines IL-2, IL-4, IL-6, IL-10, TNFα and interferon-γ were measured in plasma, although quantifiable values were obtained in a minority of the determinations. However, there was no significant difference between the groups in the proportion of quantifiable cytokine values. Dose-response relationships between PCB levels and IL-2 and IL-4 could not be evaluated. For the remaining cytokines, no significant relation with PCBs was observed. At follow-up 10 months later, a significantly higher proportion of quantifiable values were observed for IL-10 and interferon-γ within the exposed group as compared to baseline, but the plasma levels did not relate to PCB levels in a dose-dependent way and it was considered unlikely by the authors that this finding could be attributed to PCBs. The overall plasma PCB level expressed as the sum of 19 PCB congeners (including many low-chlorinated congeners) was approximately twice as high in the exposed group as in the control group. The geometric mean PCB plasma level was 2.3 µg/l (range 0.56–7.8) vs. 0.9 µg/l (range 0.45–2.2) (580 vs. 260 ng/g lipid as lipid-adjusted values). Geometric mean levels of PCBs 101, 138, 153 and 180 were 0.038, 0.46, 0.51 and 0.35 µg/l, respectively, in exposed workers. The sum of seven PCBs (geometric means), although higher in the exposed workers compared to the control group (410 vs. 230 ng/g lipid), was somewhat lower (not significant after age adjustment) than in a group of historical controls (410 vs. 580 ng/g lipid) (354) (see Table 20, Section 12.2).

In another study (82), immune parameters in 141 patients occupationally exposed to PCBs for more than 6 months were investigated (half of the patients were still exposed at the time of the investigation). Most of them were teachers, construction workers or telecommunication technicians and 90 % had been

exposed to PCBs for more than 20 years. They had also been exposed to other chemicals suspected to induce immunological impairments. The patients had different symptoms, e.g. lack of mental concentration, exhaustion, frequent common cold diseases, bronchitis and irritations of mucous membranes of the throat and nose. Lymphocyte subpopulations, *in vitro* responses to mitogens and allogeneic stimulator cells, plasma neopterin, cytokines, soluble cytokine receptors, soluble adhesion molecules, and Ig auto-antibodies were determined. Weak dose-response relationships between plasma PCB levels (PCBs 101, 138, 153 and 180) and immune parameters were found. PCBs were weakly associated with *in vitro* lymphocyte stimulation, the numbers of lymphocyte subpopulations in the blood, and titres of different autoantibody types against immunoglobulin components. However, it was stated that few associations remained significant after adjustment for multiple testing when the frequency of individuals with impaired immune parameters were related to blood levels above the mean. Patients with plasma levels of PCB 138 above the mean (> 0.7 μg/l) had more frequently undetectable IL-4 plasma levels than patients with PCB 138 levels below the mean. Patients with plasma PCB 101 levels above the mean (> 0.03 μg/l) had more often low DR+ cell counts (the HLA-DR cell surface marker) in the blood than patients with PCB 101 below the mean. The plasma levels of PCBs 138, 153 and 180 were elevated in many of the patients (means for all patients were 0.7, 1.0 and 0.6 μg/l, respectively), whereas none of the patients had levels of PCB 101 that were higher than estimated background levels. The 95 % quantiles of blood levels of PCBs 101, 138, 153 and 180 in the patients were 0.07, 1.4, 2.2 and 1.1 μg/l, respectively (see Table 20, Section 12.2). Blood levels of the various compounds (pentachlorophenol, hexachlorobenzene, hexachlorocyclohexane-α, -β, and -γ, and PCBs) were strongly correlated with one another, making it difficult to dissociate the impact of individual compounds. To avoid interference from pentachlorophenol, patients with pentachlorophenol blood levels > 10 μg/l were excluded from the study. The 9 patients with low or absent blood concentrations of the chemicals studied had higher T-lymphocyte counts (CD3), higher interferon-γ plasma levels and lower γ-glutamyl transferase plasma levels than the 40 patients with blood concentrations of all compounds above background, which provides some evidence for a cumulative effect of several weakly active compounds (82).

Langer *et al* reported significantly lower serum levels of β_2-microglobulin (a cell membrane protein involved in the regulation of the immune system response, cell-mediated immunity) in workers (n = 242) than in controls. The workers had been employed for at least 5 years at a Slovakian factory producing PCBs in 1955–1985 and were residing in a heavily PCB polluted area. The average TEQs in serum of three employees was 137.7 pg/g lipid (PCBs, PCDDs, PCDFs). Two control populations from areas much less polluted by PCBs were used (220). The same authors later reported an immunomodulatory effect, seen as an increased prevalence of thyroid antibodies and glutamic acid decarboxylase antibodies, in workers heavily exposed to PCBs (serum samples also contained PCDDs and PCDFs) (223, 224) (see also Sections 11.1.5 and 11.1.6).

In most old occupational studies, few immunological data were reported (clinical measurements of white blood cell counts and serum proteins). In one

study, total and differential white blood cell counts were determined in 194 capacitor plant workers who were exposed to Aroclors 1254, 1242 and/or 1016 for an average of 17 years. The mean area air concentration of PCBs in 1975 was 690 μg/m^3 and the average personal TWA level in 1977 was 170 μg/m^3. In 1976, clinical examinations showed some elevations in total white blood cells associated with decreased PMNs (polymorphonuclear cells, i.e. neutrophils) and increased lymphocytes, monocytes and eosinophils (19).

The proportions of positive responses to mumps (92 % vs. 89 %) and trichophyton (17 % vs. 8 %) antigen following an intradermal injection did not differ significantly in a group of 55 PCB exposed transformer repairmen as compared to 56 controls. The mean diameters of the skin reactions to mumps antigen in the two groups were identical. Personal breathing zone samples showed concentrations of PCBs ≤ 60 μg/m^3. Eight-hour TWAs of PCBs were 0.01–24 μg/m^3. The PCB patterns resembled Aroclor 1260 (100, 101). The measured total serum median values as reported in a later study (27 PCB peaks were quantified) were approximately 43 μg/l for currently exposed workers, 30 μg/l for formerly exposed workers and 13 μg/l for controls (114).

The immune status in relation to exposure to dioxin-like compounds, measured in chemical-activated luciferase gene expression (CALUX) bioassay, and to serum levels of PCBs 138, 153 and 180, was investigated in a study of 200 Flemish adolescents (PCBs 28, 52 and 101 were below the limit of detection). Very few significant associations with PCBs were seen, whereas dioxin-like compounds were related to biomarkers of immune status. An inverse association between IgGs and sum of PCBs 138, 153 and 180 ($p = 0.009$) was found (403).

Serum concentrations of POPs and the prevalence of arthritis were investigated in 1 721 adults in the National Health and Nutrition Examination Survey (NHANES) 1999–2002. PCBs were positively associated with arthritis in women, but not in men. Neither PCDDs nor PCDFs were associated with arthritis in either sex. Participants were considered to have prevalent arthritis if they answered "yes" to the question: Has a doctor or other health professional ever told you that you had arthritis? In women, odds ratios (ORs) with 95 % confidence intervals (CIs) for prevalence of arthritis across quartiles (1st quartile used as referent) were 2.1 (1.0–4.5), 3.5 (1.7–7.4) and 2.9 (1.3–6.5) for "dioxin-like" PCBs (PCBs 74, 118, 126 and 169) (p for trend 0.02) and 1.6 (0.8–3.1), 2.6 (1.3–5.1) and 2.5 (1.2–5.2) for non-dioxin-like PCBs (PCBs 138, 153, 170, 180, 187) (p for trend 0.02), respectively, after adjustment for age, race, body mass index, poverty income ratio and smoking. When single congeners were analysed separately, significant trends were seen for PCBs 74, 118, 170, 180 and 187. For subtypes of arthritis in women, rheumatoid arthritis was more strongly associated with PCBs than was osteoarthritis (231).

11.1.3 Cardiovascular effects

In recent years, it has been suggested that POPs including PCBs might contribute to the development of inflammatory diseases such as atherosclerosis (147). The possible relationship between PCB exposure and cardiovascular disease has been investigated in a number of occupational studies of which some reported a slightly, but non-significantly, increased risk for ischaemic heart disease. Mortality rates in

the occupational cohorts were compared to those in national or state total populations. Such comparisons are likely to result in an underestimation of the true risk as the general population includes sick and disabled people unable to work due to cardiovascular disease ("the healthy worker effect"). Regarding the general population, some studies suggest an association between PCBs and hypertension, but there are limitations of the studies because of the cross-sectional design. Relevant studies are described below.

A Swedish cohort of 242 male capacitor manufacturing workers exposed to PCBs for at least six months during 1965–1978 was followed from 1965 to 1991 and mortality rates were compared to national death rates. High-exposed workers had a higher standard mortality ratio (SMR) for circulatory diseases (3.3, 95 % CI 1.1–7.7) after at least five years of work and a latency of 20 years or more, but this was not observed for ischaemic heart disease (146).

Among 2 984 male hourly capacitor workers from two production plants in upstate New York, the SMR for ischaemic heart disease did not differ significantly from that of the US male population (208).

A cohort of 3 588 electrical capacitor workers exposed to PCBs 1957–1977 at an Indiana facility was followed until 1986. Mean serum PCB levels (1–4 chlorines) were 100–760 µg/l. The mortality for diseases of the heart was lower as compared to the US population. According to the authors, the healthy worker effect together with the inclusion of persons lost to follow-up could partly explain the low overall mortality of the cohort (364). The cohort comprising 3 569 workers was further followed through 1998. Cumulative PCB exposure was calculated for each worker based on job titles, job codes and era of employment. The overall ischaemic heart disease SMR did not differ significantly from that of the Indiana State population (321).

A total of 2 885 white electrical capacitor workers were exposed to PCBs and other chemicals between 1944 and 1977 in a plant in Illinois. Before 1952, chlorinated naphtalenes were used as a dielectric. In 1952, PCBs were introduced and used in large capacitors until 1979. The main exposure to PCBs was through skin contact, but airborne exposure occurred in one department. The SMR for ischaemic heart disease was 1.1 (95 % CI 0.96–1.3) for white males and lower for white females when compared to US standard rates (258).

A cohort was formed of 2 572 workers manufacturing electrical capacitors employed for at least 90 days at a New York plant during 1946–1977 or at a Massachusetts plant during 1939–1976 and who held jobs identified as having the highest PCB exposure. The SMR for ischaemic heart disease did not differ significantly from that of the US (300). Also in the total cohort of 14 458 workers with at least potential PCB exposure during 1939–1977, the ischaemic heart disease SMR was not increased (301).

Another cohort comprised 138 905 male workers employed full time at any of five US electric utility companies at any time during 1950–1986 and with a total of at least 6 months of continuous employment. The mortality for diseases of the heart was significantly lower as compared to that of the US population (250).

In a study by Broding *et al*, 562 subjects who had worked on average 14.7 years in a PCB contaminated building scored significantly higher than the control group

in subscale "cardiac complaints" on the 24-item Giessen Subjective Complaints List (GSCL-24). The subscale scores were, however, low in both groups. Multivariate analysis confirmed that work in the contaminated building influenced the intensity of complaints, although overall, thorough statistical analysis revealed no correlation of symptoms on the GSCL-24 scale and current PCB congener plasma concentrations. Several confounding variables (e.g. socioeconomic status, medication) were not controlled for. The median sum of PCBs in air was 1.28 $\mu g/m^3$. The mean plasma level (sum of PCBs 28, 52, 101, 138, 153, 180) in the exposed group was 2.6 µg/l (46).

Results from NHANES 1999–2002 (final sample size 889 persons) indicated an association between serum concentrations of five "dioxin-like" PCBs (PCBs 74, 118, 126, 156 and 169), six non-dioxin-like PCBs (PCBs 99, 138, 153, 170, 180 and 187) and four organochlorine pesticides and the prevalence of self-reported diagnosis of cardiovascular disease, but only among females. Adjustment was made for e.g. age, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, hypertension, smoking and exercise. In females, the adjusted OR for the highest quartile compared to the lowest quartile was significant (OR 5.0) for the sum of the five "dioxin-like" PCBs (p for trend < 0.01). The highest ORs (9.2 and 10.4) were seen for PCB 156 in the two highest quartiles (p for trend < 0.01). The adjusted OR for the sum of the six non-dioxin-like PCBs (females) was significant for the highest quartile (OR 3.8 and p for trend 0.02) and ORs were 9.2–13.4 for PCBs 138, 153 and 170 (all p for trend ≤ 0.01). The median serum levels (females) in the highest quartiles were 21, 91, 127 and 36 ng/g lipid, respectively, for PCBs 156, 138, 153 and 170. The authors stated that their results were in general agreement with, but stronger than, those of previous prospective cohort studies of subjects exposed to high concentrations of selected POPs in occupational or accidental settings, but emphasised that their results must be interpreted with caution, because of the cross-sectional design and use of self-reported disease (147).

The same authors (148) reported suggestive associations between hypertension in men (but not in women) and both the sum of five "dioxin-like" PCBs (PCB 74 included) and the sum of six non-dioxin-like PCBs when NHANES 1999–2002 was studied (524 participants). Adjusted ORs in the highest tertiles were 2.3 and 2.8 (p for trend 0.04), respectively. However, the only significant associations for PCBs were seen in men for PCB 156 in the 4th quartile and for PCB 74 in the 3rd quartile with ORs 3.3 and 3.5, respectively. Hypertension was defined as systolic blood pressure equal to or above 140 mm Hg or diastolic blood pressure equal to or above 90 mm Hg. Treated hypertensives were excluded.

Another study using the NHANES 1999–2002 investigated the association of 11 PCBs in serum with hypertension (2 074–2 556 participants depending on the chemical analysed). Persons were assigned to the hypertensive category if a doctor had told them that they were hypertensive, or were on antihypertensive drugs, or had a systolic blood pressure equal to or above 140 mm Hg or diastolic blood pressure equal or above 90 mm Hg. After adjustment (e.g. for age, gender, body mass index, smoking, total cholesterol), several PCBs (PCBs 74, 99, 118, 126, 138/158, 170, 187) remained significantly associated with hypertension (gender

data were not reported separately). The strongest adjusted associations were found for the dioxin-like PCBs 126 and 118. The group with serum levels of PCB 126 > 59.1 pg/g lipid had an OR of 2.4 compared to the group with levels ≤ 26.1 pg/g lipid. In the group with concentrations of PCB 118 > 27.5 ng/g lipid, the OR was 2.3 (comparison group had < 12.5 ng/g lipid) (112). In a re-evaluation using data from 2 additional years (NHANES 1999–2004) only the "dioxin-like" PCBs 74, 118 and 126 were significantly related to hypertension (113).

The general population was also studied in the city Anniston, an area close to a Monsanto plant (136). Hypertension was defined as being on antihypertensive medication, or having a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg. It was suggested that PCB exposure may be an important contributing factor in regulation of blood pressure. Total PCBs in serum (37 congeners, non-*ortho* PCBs not analysed) were measured and recorded as tertiles. The occurrence of hypertension was significantly elevated in both the 2nd (OR 1.60) and 3rd (OR 2.13) tertiles of total PCBs as compared to the 1st tertile after adjustment for age (whole study population, n = 758). There was no association of total PCBs with hypertension among those on antihypertensive medication. In individuals not on antihypertensive medication, however, a significant positive relation between serum PCB level and both systolic and diastolic blood pressure was evident after adjustment for potentially confounding variables (age, body mass index, total lipid, sex, race, smoking and exercise). ORs for the highest to lowest tertiles of total serum PCBs exceeded 3.5 for both systolic and diastolic hypertension.

Significant associations between hypertension and blood level of dioxin-like compounds were reported in a Japanese study on the general population focusing on the metabolic syndrome. The adjusted OR for dioxin-like PCBs was significantly elevated in the 4th compared to 1st quartile (OR 1.9 and p for trend < 0.01). Hypertension was defined as systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg, or self-reported history of physician-diagnosed hypertension (393) (see also Section 11.1.6).

11.1.4 Hepatic effects

Hepatic effects have been investigated in a number of studies of PCB exposed workers from the 1970s and 1980s, although hepatic endpoints are essentially limited to serum enzymes and other biochemical indices, e.g. serum lipids and cholesterol. Definite conclusions regarding human hepatotoxicity are hampered by limitations in study design of available studies such as exposure misclassification, lack of controls and lack of correction for common confounding variables (e.g. age and alcohol consumption) (19, 100). There is no clear indication that environmental low-level exposure to PCBs has caused adverse liver effects in humans (19). However, increased mortality from chronic liver disease and cirrhosis was seen in a population exposed to rice oil contaminated with PCBs/PCDFs (*Yu-Cheng*) (19, 390).

Increased levels of serum enzymes have been correlated with serum PCB levels in some of the studies. Particularly, levels of γ-glutamyl transferase, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase and/

or lactate dehydrogenase have been increased. In general, the results of the exposed groups were within the expected normal limits, or the number of persons falling outside the normal range was not significantly greater than anticipated. Increased levels of serum triglycerides and cholesterol have not been reported consistently in workers with long-term occupational exposure to PCBs. The variable results can be explained at least partially by failure to control for variables known to affect serum lipid levels. Increased urinary excretion of porphyrins has been seen in PCB exposed workers compared to control groups, although no correlations with blood/serum PCB levels were shown (19, 193).

Extensive laboratory investigations including serum liver function tests (e.g. γ-glutamyl transferase, ALAT, ASAT, alkaline phosphatase and lactate dehydrogenase) and measures reflecting microsomal enzyme induction were reported in a study of 55 transformer repairmen exposed to PCBs (predominantly Aroclor 1260) and 56 subjects never occupationally exposed to PCBs. The proportion of current alcohol drinkers did not differ significantly between groups. Serum γ-glutamyl transferase levels were not significantly different between the exposed and the control groups but were significantly and positively correlated with serum PCBs (all study participants), more strongly after adjustment for confounding variables, possibly indicating enzyme induction. γ-Glutamyl transferase was not significantly correlated with adipose tissue PCBs. Further, no correlation between serum lipids (including cholesterol, triglycerides) and serum PCBs was found. Clearance of antipyrine, a known substrate for microsomal hepatic enzymes, was determined but there was no significant difference in mean plasma half-time of antipyrine between the three groups (current and past exposed, controls), although a difference of borderline significance ($p = 0.07$) was observed between the total exposed group and the control group. There was no significant correlation between antipyrine half-time and either adipose or serum PCB concentration. PCB levels in serum and lipid tissue were at least 2–3 times higher in the presently exposed subjects than in controls. The PCB patterns resembled Aroclor 1260 (19, 99-101). The measured total serum median values as reported in a later study (27 PCB peaks were quantified) were approximately 43 μg/l for currently exposed workers, 30 μg/l for formerly exposed workers and 13 μg/l for controls (114). Personal breathing zone samples showed concentrations of PCBs ≤ 60 μg/m^3. Eight-hour TWAs of PCBs were 0.01–24 μg/m^3. There was also PCB contamination of the hands (19, 99-101).

Significant positive associations between PCB 138 and 153 plasma levels and γ-glutamyl transferase plasma levels were reported in a group of 141 patients occupationally exposed to PCBs for more than 6 months (half of the patients were still exposed at the time of the investigation). Most of them were teachers, construction workers or telecommunication technicians and 90 % had been exposed to PCBs for more than 20 years. However, confounding factors such as alcohol consumption were not controlled for and blood levels of PCBs were strongly correlated with those of other chlorinated compounds. Mean plasma levels of PCBs 138, 153 and 180 were 0.7, 1.0 and 0.6 μg/l, respectively (see Section 11.1.2) (82).

A comparison of 23 Swedish men with a high consumption of Baltic Sea fish and 20 men with virtually no fish consumption showed no significant differences

in serum levels of γ-glutamyl transferase, ASAT, ALAT, alkaline phosphatase or bilirubin. The fish eaters had elevated blood levels of PCBs, other organochlorines and methylmercury (19). Serum γ-glutamyl transferase and cholesterol were positively correlated with serum PCB levels (these associations were independent of e.g. age and alcohol consumption) in 458 residents in Alabama exposed to PCBs by ingestion of contaminated fish (containing also *p,p′*-dichlorodiphenyl-trichloroethane (DDT)). The geometric mean serum concentration of PCBs (analysed as Aroclor 1260) was 17.2 μg/l (range 3.2–158) (19, 214).

In studies of people exposed to PCBs and e.g. PCDFs by ingestion of contaminated rice oil (*Yusho* and *Yu-Cheng* incidents), increased serum levels of enzymes (indicative of microsomal enzyme induction or liver damage) as well as markedly elevated serum triglyceride levels with unchanged total serum cholesterol have been reported. Further, increased mortality from cirrhosis of the liver and from other liver diseases was seen in a cohort of 1 940 *Yu-Cheng* victims 12 years after the incident (19). In a later 24-year follow-up study of 1 823 *Yu-Cheng* subjects, increased mortality from chronic liver disease and cirrhosis was observed in the early period after exposure, but only in men (390).

11.1.5 Thyroid effects

An elevated OR for goiter was found in the *Yu-Cheng* cohort and a number of studies have examined the relationships between indices of PCB exposure and thyroid hormone status, as indicated from measurements of serum thyroid hormones (19). Findings from human studies have been conflicting (268), but some data indicate an inverse association between concentrations of PCBs and T_3 and/or T_4 in blood. Part of the inconsistency between studies might be due to exposure of participants to other endocrine disrupting chemicals and the limited possibility to isolate specific effects of PCBs (80, 329).

In a review by Hagmar, 13 relevant epidemiological studies within this field were scrutinised following a literature search for the period ranging from 1966 to 2002. The studied populations were children, adolescents or adults. According to the author, the overall impression was a lack of consistency between studies of reported correlations, nor were there any obvious inter-study dose-response associations. It was concluded that PCB exposure had not been convincingly shown to affect thyroid hormone homeostasis in humans. On the other hand, it was also stated that there were intrinsic limitations of the studies used, that comparisons between the studies were difficult and that available data did not exclude such associations (150).

One of the studies (99) dealt with in the review by Hagmar was a study on 55 male workers with a potential of occupational PCB exposure and 56 unexposed comparison workers. Total PCBs were analysed in both serum and lipid tissue, showing 2–3 times higher PCB body burdens of the presently exposed subjects. Despite the finding of a slightly lower mean value for T_4 in serum in the exposed group, there was no indication of a dose-response association after adjustment for age. There was no correlation between PCBs in adipose tissue and T_4 values. Eight-hour TWAs of PCBs were 0.01–24 μg/m^3. PCB contamination of the hands was also observed (99, 100, 114, 150).

In a recent Swedish study on workers removing old elastic PCB-containing sealants, no evidence of effects on thyroid function as measured by serum levels of total T_3, free T_4 and TSH was found. Male workers (n = 36) with at least 6 months experience of PCB removal in the two previous years (2000–2001) and a control group of matched workers (n = 32) were investigated, but no differences in the hormone levels between the groups were found. Further, combining occupationally exposed workers and controls, no significant correlations with thyroid function parameters were observed, neither for the individual PCB congeners 28, 52, 101, 118, 138, 153 or 180, nor for the sum of the seven indicator PCBs or the sum of all 19 measured PCBs. Tobacco habits, PCB background exposure, occupational history and general health were assessed by use of a questionnaire. More smokers were found in the exposed group, 39 % vs. 9 %. Eight exposed subjects and 27 controls denied using any respiratory protection. The overall plasma PCB level expressed as the sum of 19 PCB congeners (including many low-chlorinated congeners) was approximately twice as high in the exposed group as in the control group. The geometric mean of 19 PCBs was 2.3 µg/l (range 0.56–7.8) vs. 0.9 µg/l (0.45–2.2) and 580 vs. 260 ng/g lipid as lipid-adjusted values (354) (see also Section 11.1.2).

In a Slovakian study (223), clinical and laboratory signs of thyroid disorders (thyroid volume, urinary iodine, hormones and thyroid antibodies) were measured in 238 employees of a factory, which had produced PCBs (resembling Aroclor 1242) in 1955–1985, and in adolescents from the surrounding area polluted by PCBs. Controls were adults and adolescents from much less polluted areas. A significantly higher thyroid volume ($p < 0.001$) was found in the employees compared to controls matched by age and sex. Further, increased prevalences of thyroid antibodies (against thyroid peroxidase, thyroglobulin or TSH receptor) were found among employees compared to adult controls. The levels of total T_4, TSH and thyroglobulin were approximately the same in workers and controls. The prevalence of normal thyroids was significantly lower among employees who had worked in the factory for 21–35 years compared to those who had worked for 11–20 years and compared to age- and sex-matched controls. Very high levels of total PCBs in human samples from the area were still found in 1990–1994, e.g. serum levels of 1 160–9 600 ng/g lipid and average values of 12 300 ng/g lipid in adipose tissue. The most abundant congeners were 28, 118, 138, 153 and 180. The average TEQs in employees were 137.7 pg/g lipid in serum (PCBs 126 and 169, PCDDs and PCDFs) (223).

In a later Slovakian study (221), a total of 461 adults were divided in four groups according to their domicile as related to the level of environmental pollution. Three groups (n = 360) consisted of adults from an area with background pollution or from more polluted areas. One group (n = 101) consisted of long-term employees of a formerly PCB producing chemical factory subjected to high PCB exposure or subjects living in a close vicinity. The frequency of several characteristics of thyroid disorders (thyroid volume > 20 ml, hypoechogenicity (reduced ultrasound echo), solitary nodules, positive thyroperoxidase antibodies, abnormal TSH level) was investigated. Significantly increased frequencies for thyroid volume > 20 ml, hypoechogenicity and thyroperoxidase antibodies were observed in the chemical

factory employee group compared to the pooled values of the other three groups. An association between a very high PCB level in the group of employees (mean: 7 300 ng/g lipid in serum) and increased thyroid volume was found, the volumes being significantly higher than those of the three groups with lower PCB exposure (mean: 2 045 ng/g lipid in serum). Also, the thyroid volume and median levels of PCBs increased with age (all groups taken together), although the ranges of PCB values in all age groups showed very large spans. The positive association between serum PCB levels and increased thyroid volume appeared to be more pronounced for PCB 101 than for the stable PCB congeners 153 and 180 when thyroid volume in the subjects was stratified exclusively according to the levels of the PCB congeners. It was stated by the authors that the iodine intake in Slovakia had been sufficient since the early 1950s (221).

In a recent study by the same authors, serum levels of the 15 most abundant PCBs, *p,p´*-dichlorodiphenyldichloroethylene (DDE) and hexachlorobenzene were measured in 2 046 adults from two areas in Slovakia. Data were stratified into quintiles of PCB levels (n = 408–410 for each) and studied in relation to markers of thyroid effects. Upper PCB levels in serum for each quintile were 627, 906, 1 341, 2 343 and 101 413 ng/g lipid. Highly significant increases in the number of cases were seen for the following parameters (number of cases from the lowest to the highest quintile): increased thyroid volume (79/79/84/122/124), positive thyroperoxidase antibodies (83/98/88/126/116), increased free T_4 (70/84/114/104/128) and total T_3 (100/105/116/139/132), and decreased TSH (4/5/12/7/20) (222).

In a recent review, 22 epidemiological studies (published until May 2008) presenting measurements of PCB levels in biological matrices and thyroid hormone and TSH levels from adults were included (329). The studies were given quality scores and eight studies were considered as Tier I papers (Table 15). These eight studies investigated the general population and fish consumers including fishermen. The Tier I papers supported a conclusion that serum PCB levels are inversely associated with both T_3 and T_4. However, only one of the studies showed an inverse relationship with free T_4. No measurements of free T_3 were performed. For TSH, the results were mixed, indicating no relationship with PCB levels. In general, most of the Tier II papers, which included studies with methodological limitations (e.g. (100)), noted no significant associations between PCBs and TSH or thyroid hormones with the exception of T_3 (significant inverse association). In the Tier I studies, the exposure levels were transformed to a lipid basis using the concentration of serum lipid of 7.9 g/l. A significant inverse association between PCB and T_3 serum levels was seen in some, but not all, papers with PCB mean levels of 222–822 ng/g lipid. A significant inverse association with T_4 was reported in some studies with mean PCB levels of 269–848 ng/g lipid. Part of the inconsistency of the epidemiological study results may be explained by the fact that study participants were exposed to other possible endocrine disrupting chemicals. Further, many studies report only total PCBs or selected congeners or different groups of congeners, which precluded meaningful comparisons of findings across studies (329).

Dallaire *et al* studied Inuit adults (n = 623) and measured TSH, free T_4, total T_3, thyroxine-binding globulin and plasma levels of 41 contaminants including PCBs and their metabolites, organochlorine pesticides, polybrominated diphenyl ethers,

Table 15. Associations in adults from the general population between serum or plasma PCB levels and blood concentrations of thyroid and pituitary gland hormones observed in Tier I papers. Adapted from the review by Salay and Garabrant (329).

No. of PCBs	No. of subjects and gender	Sum PCBs Mean, ng/g lipid	Hormones			
			T_3	T_4	Free T_4	TSH
20	1 166 males	200 (GM)	−	↔	−	↓
	1 279 females		−	↔	−	↔
89	179 males	822 vs. 201 [a]	↓	↓	↔	↔
	51 females	305 vs. 157 [a]	↔	↓	↓	↔
89	56 males	806 vs. 204 [a]	↓	↓	↔	↓
16	124 males	269 (median)	↔	↓	−	↑
	87 females	237 (median)	↓	↔	−	↔
10	66 males	235	−	↔	−	−
1 (PCB 153)	196 males	370 (median)	−	−	↔	↔
57	341 males [b]	222 (GM)	↓	−	↔	↔
186	males + females 608 (TSH) 192 (T_4)	848 vs. 405 [a]	−	↓/↔ [c]	↔	↔

[a] Referents.
[b] From infertile couples.
[c] Inverse association for the 1st quartile of PCB level, no association in the analysis of PCBs as a continuous variable.
GM: geometric mean, T_3: triiodothyronine, T_4: thyroxine, TSH: thyroid-stimulating hormone.
↓: significant inverse association ($p < 0.05$), ↑: significant positive association ($p < 0.05$),
↔: no significant association, −: hormone parameter not assessed.

perfluorooctanesulphonate (PFOS) and dioxin-like compounds. Inverse associations were found between total T_3 concentrations and almost all PCBs congeners and their metabolites, as well as organochlorine pesticides and dioxin-like compounds. Thyroxine-binding globulin concentrations were inversely related to the less chlorinated PCBs, hydroxylated PCBs and organochlorine pesticides. Lowered TSH concentrations were associated only with the most chlorinated PCBs and hydroxylated metabolites. Some associations were also found for PFOS and 2,2′,4,4′- tetrabromodiphenyl ether (BDE-47). The authors summarised that exposure to several polyhalogenated compounds was associated with modifications of the thyroid parameters, mainly by reducing total T_3 and thyroxine-binding globulin circulating concentrations, although it was almost impossible to isolate specific effects of PCBs and their metabolites, as well as of organochlorine pesticides, on the thyroid system from epidemiological studies of this population. Further, most Inuit participants had a thyroid status within the euthyroid range (80).

11.1.6 Diabetes

It has been suggested that environmental exposure to persistent organochlorine compounds including PCBs may contribute to elevated incidence of especially type 2 diabetes. In several cross-sectional and follow-up studies of the general population, groups with higher PCB serum levels had an increased risk for diabetes, as compared to groups with lower PCB levels. However, the possibility of a reverse causality or that both PCB levels and diabetes are independently related to fat turnover cannot be ruled out. There are also some studies not showing an association between PCBs and diabetes. In a recent review (110), it was concluded that the evidence tends to support associations of dioxin-like PCBs with diabetes (type 2)

in cross-sectional studies, although there is a need for large scale prospective studies to determine if PCBs and other POPs contribute to development of diabetes. Most of the relevant studies are described below.

In a study by Langer *et al*, serum glutamic acid decarboxylase antibody values exceeded 1.20 U/ml in 40 % (97/240) of factory employees as compared to 10 % (74/704) of controls ($p < 0.001$), suggesting an immunomodulatory effect. In employees aged 51–60 years, the glutamic acid decarboxylase antibody values exceeded 1.20 U/ml in 53 % (25/47) as compared to 11 % (13/117) in age-matched controls ($p < 0.001$) (224). Such antibodies are typical markers among patients with type 1 diabetes but not for patients with type 2 diabetes (35).

Longnecker (2006) stated that relevant findings that did not support an association between diabetes and PCBs had been reported in some other studies of occupationally exposed workers. According to Longnecker (246), blood glucose concentrations were unrelated to serum PCB levels in an old study of capacitor workers. Still, a substantial number (29/194) had blood glucose levels above normal laboratory standard age- and sex adjusted ranges (based on ± 2 standard deviations from mean values) (226). Further, death from diabetes mellitus was essentially unrelated to PCB exposure in a cohort of capacitor workers (209) employed at the same facilities as those in the previous study (226). Significantly elevated SMRs (95 % CI) for diabetes were noted for female capacitor workers, but there was no information as to whether any of these women were diabetic before employment. The SMRs for diabetes were 3.1 (1.2–6.3, 7 observed deaths) in 362 ever-high-exposed female hourly workers and 3.7 (1.2–8.7, 5 observed deaths) in 184 hourly women who held a high-exposure job for 6 months or more. The SMR for diabetes was no longer significantly elevated in 122 female hourly workers who had worked in a high-exposure job for 1 year or more (209). In some other studies, no increase in mortality from diabetes mellitus was observed in capacitor manufacturing workers (300, 301) or in electric utility workers (250). However, mortality is a crude measure of diabetes.

In a prospective study, the incidence of self-reported adult-onset diabetes mellitus in a US polybrominated biphenyl cohort established in 1976 was reported. Follow-up data (n = 1 384) over 25 years showed that higher PCB serum levels in women, but not in men, were associated with increased incidence of diabetes among those without self-reported diabetes at enrolment. PCB serum measurements were available at enrolment, before the development of diabetes. Aroclors 1016, 1254 and 1260 were used as standards. The technical detection limits for PCBs were 3–5 µg/l. The serum PCB levels were grouped into 4 levels: ≤ 5, 5.1–7, 7.1–10 and >10 µg/l. An increased incidence density ratio of having adult-onset diabetes was seen in women in all three higher PCB exposure groups (> 5.1 µg/l) when compared to the reference level (≤ 5 µg/l). After adjusting for other risk factors, women in these groups had a significantly increased (2–2.3-fold) incidence density ratio of diabetes. Reverse causation was judged to be unlikely by the authors. No relationship between exposure to polybrominated biphenyls and incidence of diabetes was found (410).

In a recent study by Langer *et al*, serum levels of POPs including 15 PCBs were measured in 2 046 adults from a heavily polluted area in Slovakia. The data were

stratified into quintiles of PCB levels (n = 408–410 for each) and studied in relation to e.g. fasting glucose and insulin, cholesterol and triglycerides. Upper PCB levels in serum for each quintile were 627, 906, 1 341, 2 343 and 101 413 ng/g lipid. Increasing PCB levels (as sorted in terms of quintiles) resulted in highly significant increases in the number of cases with increased fasting glucose (no. of cases per quintile: 171/190/235/272/295), increased fasting insulin (88/86/94/105/122) and increased triglycerides (89/119/127/142/134) (222).

In a later study, ORs for prediabetes and diabetes were given with the 1st quintile serving as the reference group. The cohort (the same as in Langer, 2009 (222)) consisted of 296 patients with diabetes, 973 individuals with prediabetes and 778 individuals with normal fasting plasma glucose. Adjusted ORs for the prevalence of prediabetes were significantly elevated for PCBs in the 3rd, 4th and 5th quintiles with ORs (95 % CI) 1.5 (1.1–2.1), 2.3 (1.6–3.2) and 2.7 (1.9–3.9), respectively. Adjusted ORs for the prevalence of diabetes were significantly elevated for PCBs in the 4th and 5th quintiles with ORs 1.8 (1.05–3.0) and 1.9 (1.1–3.2). Stepwise factor selection analysis indicated that the effect of DDT on the prevalence of diabetes surpassed that of the other measured POPs (395).

Diabetes in relation to serum levels of PCBs and 3 chlorinated pesticides (including DDE) was studied in an adult Mohawk population (n = 352) living in an area near a river and close to three facilities where PCBs (primarily Aroclor 1248) had been used. A total of 101 PCBs (excluding some of the most potent dioxin-like PCBs) were measured in serum and the mean total PCB level was 5 µg/l (0.5–48) or 749 ng/g lipid (85–7 110). The levels were < 13 µg/l in 95 % of the subjects. The mean total serum levels of PCB 153 and PCB 74 were 0.7 and 0.3 µg/l, respectively. The corresponding lipid-standardised values were 104 ng/g lipid for PCB 153 and 49 ng/g lipid for PCB 74. For total PCBs, a significant association for the highest tertile (≥ 5.3 µg/l) versus the lowest tertile (< 2.8 µg/l) was obtained with an OR for diabetes of 3.9 (95 % CI 1.5–10.6), but after concurrent adjustment for the other analytes (3 pesticides) the association became non-significant. For PCB 153, the association also became non-significant after adjustment for the other analytes. For PCB 74, the OR was 4.9 (1.7–14) and 3.6 (1.0–13) before and after adjustment (calculations for wet weight) (72).

Self-reported diabetes (positive answer of having been diagnosed with diabetes) was positively associated with serum levels of DDE and some PCBs in a study of a Canadian native population. Diabetes was reported by 25 of the 101 participants. Type 1 and 2 diabetes were not differentiated, but all participants reported the age at onset of diabetes to be at least 20 years. ORs for the prevalence of reported diabetes for those in the upper 75th percentile for total sum of 8 PCBs (compared to those below the 75th (sic!) percentile) were 4.9 (95 % CI 1.3–19) and 5.5 (95 % CI 1.3–24) for wet weight and lipid-standardised values, respectively. Similarly, ORs for PCBs 74 and 153 were 4.4 and 4.9 (wet weight values) and 6.1 and 6.5 (lipid-standardised values), respectively. The sum of PCBs was 0.2–42 µg/l (mean 8.2) and 44–8 863 ng/g lipid (mean 1 384) (292).

No association between prevalent self-reported diabetes and sum of PCBs in serum (19 congeners) or years of sport fish consumption were reported in a study of 503 Great Lakes sport fish consumers. In the cohort, 61 cases of diabetes were

identified. DDE exposure and dioxin-like mono-*ortho* PCBs (PCBs 118 and 167) were associated with diabetes, but the association of the PCBs with diabetes did not remain significant after control for DDE exposure (392). The same authors investigated the associations of POP body burdens in 1994–1995 with incident diabetes in 1995–2005. DDE and 18 PCBs were analysed in serum (PCB 118 was the only dioxin-like PCB included). A total of 36 cases of diabetes were reported (data from 471 participants were used to calculate incidence rates). DDE, but not PCB 118 or sum of PCBs, was associated with incident diabetes after adjustment for age, body mass index and sex. Participants (n = 289) with known diabetes status and with repeat measurements of serum PCBs and DDE in 1994–1995 and 2001–2005 were selected for metabolism analysis. The means of the annual percent change in DDE and PCB 132/153 were calculated and were not significantly different in participants with and without diabetes. This suggested that diabetes do not affect metabolism rates of these compounds (391).

The association between serum levels of POPs and prevalence of self-reported type 2 diabetes among fishermen and their wives with high consumption of fatty fish from the Baltic Sea was investigated in a Swedish study. PCB 153 was analysed in serum from 380 subjects (196 men and 184 women, 22 diabetics in total). After confounder adjustment, PCB 153 was significantly associated with diabetes prevalence. An increase of 100 ng/g lipid corresponded to an OR of 1.2 (95 % CI 1.03–1.3, p = 0.03). Gender stratified analysis showed consistent positive associations with PCB 153 among men. The prevalences of diabetes in relation to tertiles of PCB 153 serum levels were 0/64 (≤ 290 ng/g lipid), 4/61 (> 290–475 ng/g lipid) and 8/58 (> 475 ng/g lipid) (p for trend 0.005). The trend for women was not significant, but their levels of PCB 153 in serum were lower. Diabetics also had significantly higher serum DDE levels with an increase of 100 ng/g lipid corresponding to an OR of 1.05 (95 % CI 1.01–1.09, p = 0.006). It was concluded that the study provided support that POP exposure might contribute to type 2 diabetes mellitus, although the possibility of a reversed causality could not be completely excluded (323).

In a later study (314), the focus was on fishermen's wives from the Swedish east or west coasts, 15 women with type 2 diabetes mellitus and 528 non-diabetic women of which 23 participated also in the previous study (323). PCB 153 was significantly associated with type 2 diabetes, and an increase of 100 ng/g lipid corresponded to an OR of 1.6 (95 % CI 1.0–2.7, p = 0.05). However, the association became weaker when age was included in the model. Significant positive trends were observed for PCB 153 and type 2 diabetes (p = 0.004) when the exposure variables were categorised in quartiles. Mean (5^{th}–95^{th} percentiles) serum levels of PCB 153 in women with and without diabetes were 130 (56–250) ng/g lipid and 98 (30–220) ng/g lipid, respectively. A positive association between serum levels of DDE and prevalence of type 2 diabetes was also found. The authors stated that there were no experimental data supporting that di-*ortho*-PCBs such as PCB 153 would have a diabetogenic effect by themselves, but PCB 153 serves as a good proxy marker for TCDD TEQs and the total POP-derived TEQs (314).

In a recent paper, a case-control study (371 cases, 371 controls) within a cohort of Swedish women was reported. PCB 153 and DDE were measured in stored

serum samples. For 107 out of the 371 cases, serum samples were stored at least three years before their type 2 diabetes was diagnosed. In this data set, PCB 153 and DDE were not associated with an increased risk. However, when only the 39 cases that were diagnosed at least 7 years after the baseline examination and their controls were studied, an increased risk was seen for DDE (311).

A recent prospective, nested case-control study within the Coronary Artery Risk Development in Young Adults (CARDIA) cohort indicated that some POPs including PCBs were associated with incident type 2 diabetes over a follow-up of 18 years (232). Of participants diabetes-free in 1987–1988 (year 2), 90 new cases of type 2 diabetes and 90 controls (had remained diabetes-free) were randomly selected after follow-up of 18 years. POPs measured in 1987–1988 sera were 8 organochlorine pesticides (e.g. DDT and DDE), 22 PCBs and 1 polybrominated biphenyl. Serum concentrations of individual POPs (1987–88) were divided into quartiles (from the distribution in controls) with the lowest quartile used as reference category. The levels of chlorinated POPs in 1987–1988 were much higher than current concentrations in the general population (CARDIA 2nd quartile concentrations approximated the highest quartile in NHANES subjects). POPs showed non-linear associations with type 2 diabetes risk. The associations were strongest in the 2nd quartiles of trans-nonachlor, highly chlorinated PCBs and PCB 74 (in particular before lipid adjustment), with significantly elevated ORs of 2.8, 3.2, 3.4 and 3.2 for PCBs 74, 178, 180 and 187, respectively. PCBs with some affinity to the Ah receptor (PCBs 105, 118, 156) were not clearly associated with the risk of type 2 diabetes. Further, the 16 POPs (all but 4 were PCBs) with ORs ≥ 1.5 in the 2nd quartile were summed. In order to reduce POP levels in the reference group, subjects were categorised in sextiles (with the 1st sextile used as reference group). The adjusted ORs in the 2nd sextile for the 16 POPs were 5.9 (95 % CI 1.8–19) and 5.4 (95 % CI 1.6–18) for wet weights and lipid-adjusted analyses, respectively, and the highest risk (OR 21) was seen for subjects with year 2 body mass index ≥ 30 kg/m^2. Adjusted ORs were not increased among those with body mass index < 30 kg/m^2. The results were interpreted by the authors as a low-dose effect (inverted U-shape), possibly through endocrine disruption (232).

Striking dose-response relations between serum concentrations of six selected POPs (detectable in ≥ 80 % of participants) and prevalences of diabetes (probably mainly type 2) were found in a study of 2 016 adult participants (217 diabetics) in a US study of the general population (NHANES 1999–2002). Diabetes was strongly positively associated with all six POPs, especially PCB 153, oxychlordane and *trans*-nonachlor after adjustment. Interestingly, no association between obesity and diabetes was seen among subjects with non-detectable levels of POPs. However, there were few diabetics among those with non-detectable levels of individual POPs (e.g. 10/413 for PCB 153) and in the lowest calculated concentration category for the sum of the six POPs ($< 25^{th}$ percentile) there was only 1 case in each of the body mass index groups ≥ 30 kg/m^2 (n = 129) and 25- < 30 kg/m^2 (n = 158). Serum levels of PCB 153 using percentiles among detectable values were given as 14.3 ($< 25^{th}$), 36.7 (25^{th}–50^{th}), 60.2 (50^{th}–75^{th}), 93.6 (75^{th}–90^{th}) and 164 ($> 90^{th}$) ng/g lipid. Corresponding adjusted ORs were 2.5, 4.3, 5.9, 5.9 and 6.8. The authors

stated that the findings should be interpreted with caution because of the cross-sectional nature of the study (229).

In an extended cross-sectional study, associations between serum levels of 19 selected POPs including 4 PCBs considered as "dioxin-like" (PCBs 74, 118, 126, 156) and a group of non-dioxin-like PCBs (PCBs 138, 153, 170, 180, 187) and diabetes were investigated in 1 721 persons (179 diabetics). PCDFs and PCDDs were weakly associated or not associated with diabetes, while POPs belonging to PCBs or organochlorine pesticides were strongly associated. When the five subclasses of POPs were modelled simultaneously, only "dioxin-like" PCBs and organochlorine pesticides were significantly associated with diabetes. Non-dioxin-like PCBs were not associated with diabetes. When subjects were divided into quartiles based on serum concentrations, the ORs (95 % CI) for the "dioxin-like" PCB were 8.6 (2.3–32), 16 (2.3–32) and 16 (3.4–71) compared to the lowest quartile. By use of separate models, ORs were even higher, e.g. OR 24 (7.0–84) for the highest quartile of dioxin-like PCBs. Of the individual dioxin-like PCBs, PCB 118 had the highest ORs, 5.1, 6.9, 7.5 and 13 compared to the reference level (non-detectable) (230).

The relation of serum concentrations of POPs with insulin resistance (homeostasis model assessment of insulin resistance) among 749 non-diabetic subjects was investigated using the same dataset. Some 19 POPs (five subclasses) including 4 "dioxin-like" PCBs and 5 non-dioxin-like PCBs were selected. Significant associations with elevated insulin resistance were only found for organochlorine pesticides among subclasses but were also found ($\geq 75^{th}$ percentile) for two non-dioxin-like PCBs, PCBs 170 and 187, although not for PCB 153. The authors hypothesised that chlordane may be the most important POP involved in the pathogenesis of type 2 diabetes (228).

Dirinck *et al* investigated the associations between serum levels of POPs (including PCBs 138, 153, 170 and 180) and the prevalence of obesity. Obese (n = 98) and lean (n = 46) participants from the general population were examined (12 obese and 1 lean person had type 2 diabetes). An inverse relationship (Spearman rank correlation) between weight or body mass index and serum levels of all four individual PCBs or the sum of the four PCBs was found. Further it was reported that PCBs 153, 170 and 180 and sum of the four PCBs did correlate in a significantly inverse manner with fasting insulin, and similarly so PCBs 170 and 180 and sum of the four PCBs with insulin resistance (homeostasis model assessment). However, no significant correlation between fasting glucose and any of the PCBs could be established. The sum of the four PCBs in the entire group was 24–827 ng/g lipid (median 191) (97).

In several studies, an association between high dioxin burden and increased risk of type 2 diabetes or modified glucose metabolism has been indicated (72, 323). The association of PCB 126, hexachlorodibenzo-*p*-dioxin and DDT with diabetes was evaluated in a large study using data from the NHANES 1999–2002 population (persons presumed to have type 1 diabetes were excluded from the analyses). Relationships with diagnosed or undiagnosed diabetes and total diabetes were tested. All three compounds were significantly associated with diagnosed diabetes and PCB 126 and DDT also significantly with undiagnosed diabetes. An OR of 2.6 (95 % CI 1.3–5.0) was reported for those having a PCB 126 blood concentration

> 84 pg/g lipid compared to those having a PCB 126 concentration ≤ 31 pg/g lipid when all the three chemicals were included in a combined model for total diabetes. The authors concluded that the results suggest that elevated levels of PCB 126 and DDT may contribute to the development of diabetes, although it cannot be ruled out that persons with diabetes retain more of those pollutants than persons not having diabetes (111).

Uemura *et al* investigated associations between environmental exposure to dioxin-like compounds (including PCBs) and prevalent diabetes in the general population in Japan (n = 1 374, 65 subjects were defined as diabetics). Haemoglobin A1c in plasma (a marker for diabetes) correlated with the accumulated TEQs of PCDDs/PCDFs, dioxin-like PCBs and total dioxins. The median TEQs for sum of 12 dioxin-like PCBs and for total dioxins in blood were 7.6 and 20 pg TEQs/g lipid, respectively. The 3rd and 4th quartiles of dioxin-like PCBs had adjusted ORs of 3.1 (95 % CI 1.2–8.8) and 6.8 (95 % CI 2.6–20), respectively (the 1st plus 2nd quartiles were defined as reference). It was not possible to distinguish between type 1 and type 2, but most of the diabetics probably suffered from type 2 diabetes (394). The same authors also studied the relationship between dioxin-like compounds and metabolic syndrome (160 subjects were defined as having metabolic syndrome, of which 38 also had prevalent diabetes and were excluded). All of the TEQs (for PCDDs/PCDFs, PCBs, and total) were associated with the prevalence of metabolic syndrome. The OR was 7.3 (95 % CI 2.9–20) for dioxin-like PCBs with ≥ 12.9 TEQs, compared to the referent category with < 4.3 TEQs in adjusted analyses. Further, ORs for the dioxin-like PCBs increased from 1st to 4th quartiles (p for trend < 0.01) (393).

A relationship between insulin sensitivity and exposure to PCBs (but not PCDDs or PCDFs) was reported in a study from 2008. Seventeen dioxins (PCDDs/PCDFs) and the 12 dioxin-like PCBs were measured in serum from 40 non-diabetic pregnant women. Three specific PCB congeners, PCBs 123, 126 and 169 (expressed as TEQs), were significantly associated with decreasing insulin sensitivity after adjustment for age and pre-pregnancy body mass index. Also, insulin sensitivity was predicted by the sum of TEQs for PCBs (mean value 5.2 pg TEQs/g lipid), but not by TEQs of PCDDs or PCDFs or total TEQs (adjusted by age and pre-pregnancy body mass index) (62).

In a 24-year follow-up study investigating type 2 diabetes of the *Yu-Cheng* cohort, the diabetes risk (compared to reference subjects) was significantly increased for women (OR 2.1, 95 % CI 1.1–4.5) but not for men after considering e.g. age and body mass index. Further, *Yu-Cheng* women diagnosed with chloracne had an adjusted OR of 5.5 (95 % CI 2.3–13.4) for diabetes compared to those who were chloracne free (406). Markedly elevated serum triglyceride levels were seen in the victims of *Yu-Cheng* and *Yusho* poisoning incidents. However, they were exposed to dioxin-like PCDFs in addition to PCBs (19).

11.1.7 Some other endocrine/metabolic effects

In a Slovakian study, 150 individual male blood samples from residents of a PCB contaminated area and from a reference area were collected. Seventeen PCBs were determined including the common congeners 138, 153 and 180 and dioxin-

like congeners, e.g. PCBs 105, 118, 126 and 156. The total hexane/diethyl ether extracts of serum samples, containing both endogenous steroids and POPs, showed significant oestrogenic responses in the oestrogen receptor CALUX assay. Dioxin-like activities measured in the POP fractions ranged from 0.2–2.9 pg TEQs/ml. Weak oestrogenic or antioestrogenic activities were found in the fractions of POPs but only in part of the samples. Antioestrogenic activity was detected more frequently in the samples from the PCB-polluted region (in 17/75 samples). The total oestrogenic activity was moderately decreased, while the dioxin-like activity was increased in samples with high PCB levels (the 4th quartile) ranging from 13.9 to 175.5 µg/l serum (i.e. 1 866–32 509 ng/g lipid). The levels of 17β-oestradiol decreased (non-significantly) in the 4th quartile (294).

The relationship between serum concentrations of testosterone and levels of PCBs (12 individual PCBs, total PCBs, several groups of PCB congeners) or three chlorinated pesticides was studied in an adult Mohawk population. Serum samples from 257 men and 436 women were analysed for 101 PCBs, hexachlorobenzene, DDE and mirex. Testosterone concentrations in males were inversely correlated with total PCB concentrations, whether using wet weight or lipid-adjusted values. The OR (95 % CI) of having a testosterone level above the median was 0.17 (0.05–0.69) for adjusted total wet weight PCBs (highest vs. lowest tertile). Testosterone levels were significantly and inversely related (by use of logistic regression) to concentrations of PCBs 74, 99, 153 and 206 (ORs 0.15–0.33) but not to concentrations of PCBs 52, 105, 118, 138, 170, 180, 201 and 203. Inverse relations were also found for most PCB groupings (mono-, di-, tri/tetra-*ortho*-PCBs, dioxin-like PCBs (TEQs), ORs 0.30–0.35), but not for the group of non-persistent potentially oestrogenic congeners (PCBs 31, 44, 49, 52, 70). Testosterone levels in females were not significantly related to serum PCBs. Hexachlorobenzene, DDE and mirex were not associated with testosterone levels neither in men nor in women. The mean (range) level of total PCBs in men was 5.9 µg/l (1.5–49) or 953 ng/g lipid (217–7 908). The medians for serum testosterone in the highest PCB tertiles were around 400–430 ng/dl. The normal reference values in men are 260–1 600 ng/dl (137) (see also Section 11.4.1).

Hormonal status of 14–15-year old male adolescents (n = 887) was studied in relation to internal exposure to pollutants. Serum concentrations of testosterone, free testosterone, oestradiol and free oestradiol, and the aromatase index showed significant positive associations with serum levels of the sum of three marker PCBs. A doubling of serum concentrations of marker PCBs was associated with an increase of 16.4 % in serum testosterone concentration and with an increase of 7.4 % of 17β-oestradiol. The sum of marker PCBs (PCBs 138, 153 and 180) in serum as median (10th–90th percentile) was 80 ng/g lipid (43–141). Associations between biological effects and internal exposures in terms of regression coefficients were stronger at exposures below the median than at exposures above the median. The authors stated that the results of this study differed from other published data (e.g. studies on adult men and on pubertal boys with prenatal exposure to PCBs), and suggested that this might at least partly be due to the low serum PCB concentrations in this study (96). Later, data were presented regarding sexual maturation in relation to the levels of measured compounds in the 887 boys

and 792 girls. In boys, genital development (having reached at least stage 3) was significantly and positively associated with the sum of the three PCBs in serum after adjustment for the other pollutants (OR 2.2, 95 % CI 1.2–4.3, p = 0.011). In girls, the probability of having reached menarche was less (menarche later than the median) if serum concentrations of marker PCBs were higher. The sum of the three PCBs in girls as medians (10^{th}–90^{th} percentile) was 53 (30–98) ng/g lipid (90). The results are in contradiction with previous findings as was acknowledged also by the authors. In earlier studies, either no effect on pubertal stages in boys was reported or serum PCB concentrations were associated with a delay in pubertal development. In girls, exposure to oestrogenic PCBs was associated with a greater probability of having reached menarche in one study (see below), whereas age at menarche was not related to total PCBs in some other studies (Section 11.4.2.5).

Denham *et al* examined the relationship between menarche and levels of common environmental pollutants in blood of 138 Mohawk girls 10–16.9 years of age. The 16 PCBs with > 50 % rate of detection were included in the analysis and categorised into 3 groups (according to Wolff *et al*) (426), i.e. oestrogenic/neurotoxic (PCBs 52, 70, 101, 187), antioestrogenic/dioxin-like (PCBs 74, 105, 118 and 138) and enzyme-inducing (PCBs 99, 153 and 180) PCBs. Also DDE, hexachlorobenzene, mirex, lead and mercury were considered. Exposure to oestrogenic PCB congeners was associated with a greater probability of having reached menarche after adjustment for age, socioeconomic status and exposure to other toxicants. A 100 % increase of oestrogenic PCBs above the geometric mean, from 0.12 to 0.24 µg/l, was associated with 8.4 times greater odds of having reached menarche. As the levels of oestrogenic PCBs increased, the predicted probability of 12-year-old Mohawk girls having reached menarche increased from 52 % at the 25^{th} percentile to 69 % at the mean and to 86 % at the 75^{th} percentile. No relationship was observed between menarche and the other PCB groupings (i.e. antioestrogenic and enzyme-inducing PCBs) (92).

In a prospective study of a US cohort, time to menopause was investigated in relation to serum levels of PCBs and polybrominated biphenyls (PBBs) at enrolment during the late 1970s. The menopausal status was assessed by telephone interviews in 1997 and 320 (302 analysed for PCBs) out of 791 participants were classified as postmenopausal. The serum PCB concentrations were measured as Aroclor 1254 (level of detection 5 µg/l) and were categorised as ≤ 5, > 5–11 and ≥ 11 µg/l. The median PCB level was 5 µg/l (range: non-detectable to 78 µg/l). No association was found between PCB or PBB exposure and time to menopause (36).

The urinary concentrations of 17-ketosteroids and 17-hydroxycorticosteroids were significantly lower in a group of 15 residents of a polluted area near a chemical factory producing organochlorine compounds including PCBs than in a control group. There was also significantly fewer sulphonated 17-hydroxycorticosteroids in the subjects exposed to PCBs as compared to the controls, while the percentage of sulphonated steroids was lower for both 17-ketosteroids and 17-hydroxycorticosteroids in the PCB exposed subjects. The factory was in operation from 1930s to the 1980s. Totally 24 PCBs were determined in blood and the mean blood level in the exposed group was 61.9 µg/l (range 17.5–138) as compared to 3.2 µg/l (range 0.8–10.4) in the control group (318).

A significant inverse correlation between adipose tissue PCB concentration and 17-hydroxycorticosteroid excretion in urine was reported in the study by Emmett *et al* (100), possibly reflecting subtle metabolic effects of PCBs. Personal breathing zone samples showed PCB concentrations ≤ 60 μg/m^3. TWAs (8-hour) of PCBs were 0.01–24 μg/m^3. There was also PCB contamination of the hands. The PCB patterns in serum resembled Aroclor 1260 (19, 99-101). The measured total serum median values as reported in a later study (27 PCB peaks were quantified) were approximately 43 μg/l for currently exposed workers, 30 μg/l for formerly exposed workers and 13 μg/l for controls (114).

11.1.8 Bone effects

Recent epidemiological studies have yielded inconsistent results regarding whether environmental organochlorine exposure has an effect on bone properties (173). In 153 peri- and postmenopausal Inuit women with high organochlorine exposure, no significant relationship between osteoporosis-related ultrasound bone measurements and PCB 153 levels in plasma was seen after adjustment for potential confounding variables. Concentrations of PCBs 105 and 118 were not associated with the measured parameters in multivariate models, whereas significant associations were noted for PCB 156. The authors stated that this finding may be due to chance and needs to be replicated in another study. Fourteen PCB congeners (including PCBs 105, 118, 138, 153, 156 and 180) were measured and the sum of these was 341–7 384 ng/g lipid (geometric mean 2 051 ng/g lipid). The geometric mean plasma levels for some of the PCBs were 23 (PCB 105), 122 (PCB 118), 579 (PCB 153), and 77 ng/g lipid (PCB 156) (77).

Glynn *et al* studied bone mineral density in 115 men from the general Swedish population. They measured ten PCBs and some other persistent organochlorines in serum. The mean serum levels of the most abundant PCBs were 42 (PCB 118), 142 (PCB 138), 294 (PCB 153), 23 (PCB 156) and 216 (PCB 180) ng/g lipid, respectively, and between 4.2 and 10 ng/g lipid for five other measured PCB congeners (PCBs 28, 52, 101, 105, 167). Multivariate regression analysis showed no significant associations between bone density variables and sum of PCBs. Also, no consistent concentration-dependent changes were found in adjusted means of bone variables when serum concentrations of single substances or the sum of PCBs were divided into quartiles (133).

In another Swedish study (400), 196 fishermen and 184 fishermen's wives from the Swedish east coast were investigated. Measurements of bone mineral density and biochemical biomarkers in serum of osteoblastic and osteoclastic functions were done. After adjustment for age and body mass index, no associations with PCB 153 were shown. Median values for PCB 153 in serum were 370 and 240 ng/g lipid in men and women, respectively. The authors concluded that the results did not provide any support for the hypothesis that the current exposure levels to persistent organochlorine compounds constitute a hazard for impaired bone metabolism in the general Swedish population (400). Further, in a subset of 53 women (those with the highest and lowest bone mineral density), PCB 153, 4-hydroxy-PCB 107, 4-hydroxy-PCB 146 and 4-hydroxy-PCB 187 were analysed in serum. No associations were found between bone mineral density or biochemical markers

of bone metabolism and the analysed compounds. PCB 153 represented about 25 % of total PCB, suggesting a total PCB serum concentration of 280–2 500 ng/g lipid in the cohort (415).

In a recent study, Hodgson *et al* investigated a population with elderly (≥ 60 years of age) men (n = 154) and women (n = 167) living near the Baltic coast, close to a river contaminated by PCBs. The mean levels of PCB 118 were 0.2 µg/l (range: < limit of detection–1.4) in men and 0.2 µg/l (< limit of detection–1.2) in women. The concentrations of the other four measured dioxin-like PCBs were lower. Expressed as TEQs, the mean blood concentrations of these mono-*ortho* PCBs (PCBs 105, 118, 156, 157 and 167) for men and women were 0.012 pg TEQs/ml (range 0.002–0.067) and 0.013 pg TEQs/ml (range 0.003–0.053), respectively. The mean of the sum of PCBs 138, 153 and 180 was 2. 7 µg/l (range 0.4–9.0) in men and 2.6 µg/l (range 0.7–7.0) in women. The corresponding mean levels for PCB 153 were 1.3 µg/l (range 0.2–4.4) and 1.3 µg/l (range 0.3–4.6). Multivariate linear regression analysis showed that none of the organochlorines studied was significantly associated with bone mineral density in men when entered into the model individually, whereas PCB 118 was positively associated with bone mineral density in women. When the organochlorine variables were entered stepwise into the model, PCB 118 was inversely associated and the sum of PCBs 138, 153 and 180 was positively associated with bone mineral density in men. Dose-response relationships for risk of low bone mineral density were studied by dividing data into tertiles. In men, ORs (95 % CI) were 1.5 (0.5–4.0) and 2.1 (0.6–7.1) compared to the lowest tertile for PCB 118. When analysed as a continuous variable, the OR was 1.06 (1.01–1.12) for every 10 pg/ml (173).

11.1.9 Neurological effects

The main focus in human studies of nervous system effects following PCB exposure has been on neonates and young children (19). There are also some studies that suggest such effects in workers occupationally exposed to PCBs. In these studies, the PCB exposure was very high and heating/explosion was sometimes mentioned, and thus, exposure to pyrolysis products such as PCDFs may have occurred. A sex difference for some effects on the nervous system was found in some of the studies (women seemed to be more sensitive than men) (7, 19, 352, 356, 367, 370). Further, various neurological symptoms have been reported in adult victims of the *Yu-Cheng* and *Yusho* incidents and cognitive deficits in women were reported recently for one of these populations. However, these populations were also exposed to e.g. PCDFs (19, 240). Studies on the general population (e.g. fish eaters) do not allow firm conclusions regarding effects of PCBs on the nervous system, especially since there has been exposure to many other compounds as well.

In a case report, three workers with considerable skin exposure to PCBs (in particular to Clophen A 30) while repairing or dismounting transformers (exposure time 4–20 years) presented with distal-symmetrical sensorimotor polyneuropathy as well as encephalopathy. Two of the cases also suffered from chloracne and irritation of mucous membranes (the PCB blood level of one case was 4 500 µg/l). The standard of occupational hygiene was very poor and heating of

the equipment was reported. Clophen A 30 consists mainly of PCBs with a low degree of chlorine substitution (di-, tri- and tetrachlorobiphenyls) (7).

Nerve lesions were also found in workers after PCB exposure (mainly di-, tri- and tetrachlorobiphenyls and/or their degradation products) during an accident when capacitors exploded and in the following cleaning work. The first air concentrations were measured about 5.5 hours after the explosion and the highest concentrations at that time were 8 000–16 000 μg/m^3. Nausea, intense perspiration and headache were acute symptoms, which cleared quickly. Later, some of the workers complained of e.g. pin and prick sensations, itching or odd temperature feelings in their arms or legs. The 15 men with the greatest exposure were studied neurophysiologically 2 and 6 months after the explosion and the results were compared to 30 unexposed workers. A reversible, slight impairment of the peripheral nerves was noted, mainly in the distal portions of sensory nerves where the conduction velocity and the amplitude of the sensory action potentials were decreased (356).

Approximately 50 % of workers exposed to various Aroclors at a capacitor manufacturing plant for more than 5 years complained of headache, dizziness, depression, fatigue, memory loss, sleeplessness, somnolence and nervousness (the prevalence of the symptoms was not compared to a control group). Routine neurological examination did not reveal any remarkable prevalence of abnormalities. Extensor weakness was observed in 6 of the workers (1.8 %) and one worker presented tremor at physical examination. Other complaints from the workers in this study were e.g. chloracne, hyperpigmentation and irritation. Area concentrations were up to 11 000 μg/m^3. In addition to inhalation exposure, there was potential for skin contact and ingestion (19).

In another study, a significant positive correlation between symptoms (questionnaire response) suggestive of altered peripheral sensation (tingling in the hands) and increasing concentrations of low-chlorinated PCBs in serum were reported. Overt clinical dysfunction was absent, but no further details were reported (only a brief physical examination was performed). The PCB components were quantitated as lower chlorinated and higher chlorinated biphenyls by comparing with Aroclors 1242 and 1254, respectively. Mean serum concentrations of the low-chlorinated PCBs among workers at the electrical equipment manufacturing plant ranged from about 8 to 50 times background levels in the community. The mean serum levels of the high-chlorinated PCBs were about 2–4 times higher than background levels. Geometric mean serum levels of 502 μg/l (range 210–3 330) of low-chlorinated PCBs (≤ 4 chlorine atoms) and 44 μg/l (20–250) of high-chlorinated PCBs (≥ 5 chlorine atoms) were found in 14 workers in an area of presumed high exposure. Community residents (n = 89) had geometric mean values of 11.6 and 12.8 μg/l. TWA personal air sample concentrations of PCBs in some high-exposure areas were up to 264 μg/m^3 (median 81 μg/m^3). Also, skin contamination by PCBs was indicated (367).

In a group of workers occupationally exposed to rather low air levels of Aroclors, frequent headaches, insomnia, and memory problems were significantly more prevalent compared to controls, as reported in a questionnaire, but the authors supposed that the symptoms were not related to PCBs. Breathing zone sample PCB

concentrations were ≤ 60 μg/m^3 and 8-hour TWA concentrations of PCBs 0.01–24 μg/m^3 (in most cases below 13 μg/m^3). Also, PCB contamination of workplace surfaces and of the hands was noted. The measured total serum median values (27 PCB peaks were quantified) were approximately 43 μg/l for currently exposed workers, 30 μg/l for formerly exposed workers and 13 μg/l for controls. The PCB patterns resembled Aroclor 1260 (101, 114).

A large retrospective mortality study of 17 321 PCB exposed workers investigating neurodegenerative diseases has been published. The aim of the study was to determine whether mortality from Parkinson's disease, amyotrophic lateral sclerosis (ALS) or dementia was elevated compared to the US population. All workers had at least 90 days employment in 1 of 3 electrical capacitor plants using PCBs from the 1940s to the 1970s. PCB serum levels from a sample of these workers in the 1970s were approximately 10 times the level of community controls and the most highly exposed workers had levels approximately 50 times higher than controls. No overall excess of Parkinson's disease, ALS or dementia in the PCB exposed cohort was seen. However, sex-specific analyses revealed that women had an excess of ALS (SMR 2.3, 95 % CI 1.1–4.2, 10 deaths). Furthermore, among highly exposed women (defined by a job-exposure matrix) an excess of Parkinson's disease (SMR 3.0, 95 % CI 1.1–6.4, 6 deaths) and dementia (SMR 2.0, 95 % CI 1.1–3.4, 14 deaths) was seen. It was concluded that the data were limited due to small numbers and reliance on mortality rather than incidence data, but were suggestive of an effect of PCBs on neurodegenerative disease for women. It was also stated that a strong inverse relationship between current serum PCB levels and dopamine transporter density (a marker of substantia nigra neuronal death) was found among 12 female ex-workers, whereas no relationship among a larger number of male ex-workers was seen (370).

Eighty-nine former capacitor workers (50 men and 39 women) underwent (^{123}I) β-CIT SPECT (2β-carbomethoxy-3β-(4-iodophenyl)tropane single photon emission computerised tomography) imaging to estimate basal ganglia dopamine transporter density and the result was investigated in relation to serum PCB concentrations. This population represents one of the most highly exposed in the US and the majority of workers were exposed "only" to PCBs. In total, 27 PCB congeners and 9 organochlorine pesticides were determined in serum. Current total serum PCB concentrations (geometric mean) in men and women were 1 010 and 950 ng/g lipid, respectively. An inverse relationship between lipid-adjusted total serum PCB concentrations and striatal dopamine transporter densities was found in female, but not male, workers in the absence of differences in serum PCB concentrations. Similar relations were also seen between total serum PCB concentrations and either putamen or caudate β-CIT densities. However, the data demonstrated a maximal reduction of between 20 and 25 % in striatal β-CIT binding in PCB exposed women and it was stated that a reduction of this magnitude is unlikely to be associated with clinical signs of parkinsonism (352).

Subjects (n = 562) who had worked for an average of 14.7 years in a PCB contaminated building scored significantly higher complaint values on the 24-item GSCL-24 (subscales "exhaustion" and "limb complaints") than the control group. Multivariate analysis confirmed that work in the contaminated building influenced

the intensity of complaints, although overall, thorough statistical analysis revealed no correlation between symptoms on the GSCL-24 scale and current PCB congener plasma concentrations. The mean plasma concentrations in the exposed and control groups were 0.12 vs. 0.02 μg/l for PCB 28, and 0.02 vs. 0.004 μg/l for PCB 52. The mean value of PCB sum in plasma in the exposed group was 2.6 μg/l. The median sum of PCBs in air was 1.28 $\mu g/m^3$. Several confounding variables (e.g. socioeconomic status, medication use) were left out in the study (46).

No significant differences in subjective health complaints were seen in pupils attending a contaminated school using the GSCL for children/adolescents (e.g. exhaustion, pains in limbs and cold symptoms were assessed) compared to controls. Median concentrations in plasma for PCBs 28, 52 and 101 were 0.006, 0.009 and 0.005 μg/l, respectively. The values for PCBs 138, 153 and 180 were much higher but not significantly different from controls. The total PCB level in plasma (95^{th} percentile) was around 1 μg/l in both groups. Air levels of PCBs 28, 52 and 101 were 0.004–0.6, 0.04–2.3 and 0.003–1.1 $\mu g/m^3$, respectively. Total concentrations (sum of six indicator congeners × 5) ranged between 0.7 and 21 $\mu g/m^3$ (median 2.0 $\mu g/m^3$) (237).

Neuropsychological functioning of a group of 50–90-year-old fish-eaters (n = 101) exposed to PCBs through fish consumption was assessed and compared to a group of non-fish-eaters (n = 78). No significant reduction of hand steadiness (Static Motor Steadiness Test) or significant effect on visual-motor coordination (the Grooved Pegboard Test) was revealed for PCBs or DDE. Indeed, scores on the hand steadiness improved slightly as PCB/DDE exposure increased. Serum levels of PCBs (16 vs. 6.2 μg/l) and DDE were significantly elevated in the fish-eaters. Levels of lead and mercury were low in both groups but were slightly higher in the fish-eaters (19).

In a later study, a battery of cognitive tests including tests of memory and learning, executive function and visual-spatial function was administered to 180 subjects (101 fish-eaters, 79 non-fish-eaters). Blood were analysed for PCBs and 10 other contaminants. Impairments in memory and learning were reported in the fish-eaters, whereas executive function was not impaired. After controlling for potential confounders, PCB but not DDE exposure was associated with lower scores on measures of memory and learning. These included the Weschler Memory Scale verbal delayed recall, the semantic cluster ratio, and list A trial 1 from the California Verbal Learning Test. In contrast, executive and visual-spatial function was not impaired by exposure to PCBs or DDE. The most striking effect of PCB exposure was the relationship between higher PCB exposure and delayed recall on the logical memory portion of the Weschler Memory Scale. Participants with serum PCB concentrations in the upper quartile (13.9–75 μg/l) scored on average about 2 points lower (9.67 vs. 7.66) than those in the lowest quartile (up to 4.6 μg/l). Still, the authors stated that it would be prudent to interpret the findings with caution until they had been replicated in another cohort (334).

Fitzgerald *et al* evaluated neuropsychological status and PCB exposure among 253 adults (127 men and 126 women, age 55–74 years) living along a partly contaminated river. Thirty PCB congeners were measured and their sum calculated as total PCBs. In addition, 9 dioxin-like PCBs were measured in serum and TEQs

were calculated. The mean serum total PCB concentration was 3.6 µg/l (537 ng/g lipid) and the mean PCB TEQ concentration was 34.2 pg/g lipid. A neuropsychological test battery of 34 tests capable of detecting subtle deficits in memory and learning, executive function, visual and spatial recognition, reaction time, motor function, affective state and olfactory function was used. Few variables were affected and it is possible that the significant observations were due to chance because of multiple statistical comparisons. After adjustment for potential confounders, an increase in serum total PCB concentrations from 250 to 500 ng/g lipid was associated with a 6 % decrease in verbal learning (California Verbal Learning Test). The deficits were limited to the highest PCB quartile and were strongest among men 55–60 years of age. Also, a 19 % increase in depression symptoms (BDI, Beck Depression Inventory) was found (250–500 ng/g lipid). The scores rose in both the 3rd and 4th quartile and the correlation was strongest for women 55–60 years of age. On the contrary, performance improved by 9 % as serum PCBs increased from 250 to 500 ng/g lipid in a test of visual immediate recall (Weschler Memory Scale). For single congeners, significant inverse associations were apparent for PCBs 105, 118, 138, 170, 180 and 194 in the verbal learning test, and for PCBs 153, 170, 180, 183, 187 and 194 as well as PCB TEQs in the test for depressive symptoms. The low-chlorinated PCBs 28, 74 and 99 were not correlated to any of the tests (121).

A neuropsychological evaluation of native American adults (Mohawks, n = 336) who were exposed to PCBs by environmental contamination was recently reported (149). The median serum PCB concentration was 2.2 µg/l (range 0.2–25). The neuropsychological functioning was assessed by a battery of 18 tests (effective sample size: 275–283). The measured variables represented clusters of memory, motor behaviour and executive functioning. Different statistical analyses were performed and spline regression models were fitted to the latent variables of memory, motor function and higher-order executive functioning. PCBs were significantly related to outcome variables in the domains of executive functioning, motor functioning and memory. After adjusting for age, gender and education, the analyses revealed a threshold effect of PCBs at approximately 2 µg/l. An age-PCB-interaction effect was also observed for several variables, which suggest that the threshold effect was largely confined to the age range 40–79 and was not observable in the 18–40 year-old group. However, mean performance scores across the entire spectrum of neuropsychological variables were well within normal limits compared to normative groups.

Various neurological symptoms (numbness, weakness, neuralgia of limbs, hypoesthesia and headache) and reduction in sensory and motor nerve conduction velocities were reported in adult victims of the *Yusho* and *Yu-Cheng* incidents (19, 188). Among elderly women in the *Yu-Cheng* cohort, dose-dependent neurocognitive deficits in certain aspects of attention, visual memory and learning ability were reported. In exposed men, all test results were similar to the reference group (240). Since the victims were also exposed to PCDFs and other chlorinated chemicals, the findings cannot be solely attributed to PCBs (19, 188).

11.2 Mutagenicity and genotoxicity

Available information on *in vivo* genotoxic effects of PCBs in humans is scarce. Workers with a PCB exposure for over 10 years in a PCB production unit in Czechoslovakia had an increased frequency of aberrant peripheral lymphocytes (3.4 %). In the workers exposed to PCBs for less than 10 years, no significant increase in numbers of aberrant cells was observed and sister chromatid exchanges in peripheral lymphocytes were at control levels (202). The control and exposed groups were matched regarding smoking and alcohol drinking habits, but the exposed workers were also exposed to benzene, which is a known carcinogen (19).

An association between the percentage of sperms showing DNA fragmentation (%DNA fraction index (DFI)) and serum levels of PCB 153 was seen in sperm samples from Swedish fishermen. A significantly lower %DFI was found in the lowest PCB 153 quintile (< 113 ng/g lipid) compared to the other quintiles ($p < 0.001$) and this effect remained when age was included in the model ($p = 0.006$). The four highest exposed quintiles (> 113 ng/g lipid) had 41 % (95 % CI 11–78) higher %DFI than the lowest exposed quintile. The %DFI did not differ from each other in these groups (312). In a cross-sectional study involving 707 adult males (four cohorts) including the Swedish fishermen, it was shown that %DFI values of sperms increased with increasing serum levels of PCB 153. By considering all 514 European men, an increasing risk with increasing level of PCB 153 across all exposure ranges emerged, reaching statistical significance in the highest exposed group (> 401 ng/g lipid). However, no association between PCB 153 and %DFI was found among Inuit men (368) (see also Table 16, page 112).

In a recent study, biomarkers for genotoxicity were investigated in relation to levels of PCBs (PCBs 99, 118, 156, 170 and the sum of PCBs 138, 153 and 180) and other pollutants in whole blood, serum and/or urine from residents from areas with different types of pollution in Belgium. Among the reported findings were significant positive correlations between levels of micronuclei and DNA strand breaks (comet assay) in peripheral blood cells and serum levels of PCB 118 (86).

11.3 Carcinogenic effects

Overall evaluations

The overall evaluation of carcinogenicity of PCBs (based on human and animal studies) made by IARC in 1987 was "probably carcinogenic to humans" (Group 2A), although the evidence for carcinogenicity to humans was stated to be "limited" (186). PCBs were classified without distinction between dioxin-like and non-dioxin-like congeners. Information on the possible carcinogenic risk of human exposure to PCBs came from studies of occupational populations and of populations exposed accidentally. IARC concluded that the available studies suggested an association between cancer and exposure to PCBs and that the increased risk of hepatobiliary cancer emerged consistently in different studies. The evidence was considered to be limited since the numbers of cases were small, dose-response relationships could not be evaluated and the role of compounds other than PCBs could not be excluded (186). Recently, IARC classified PCB 126 as a human carcinogen (Group 1) on

the basis of mechanistic information and animal data. There is strong evidence for an Ah receptor-mediated mechanism and PCB 126 is a complete carcinogen in experimental animals (24).

In 1997, US EPA stated that the human data regarding PCBs were inadequate but suggestive of carcinogenicity (399).

ATSDR (2000) examined some 50 studies published since 1976. The carcinogenicity of PCBs was investigated in retrospective occupational cohort studies (mainly capacitor workers) using cancer mortality as endpoint, and in case-control studies of the general population examining associations between serum or adipose tissue PCB levels and cancer risk (mainly breast cancer). Many of the studies had methodological limitations. Overall, it was concluded that the human studies provided some evidence that PCBs are carcinogenic. It was assessed that some data suggested that occupational PCB exposures were associated with site-specific excess of cancer, particularly in the liver, biliary tract, intestines and skin (melanoma), whereas there was no clear association for cancer in other tissues, including the brain, haematopoietic and lymphatic systems. Case-control studies of the general population were considered inconclusive with respect to associations between PCB exposure and risk of non-Hodgkin's lymphoma (NHL) or breast cancer, although there were preliminary indications that particular subgroups of women might be at increased risk for breast cancer (19).

Based on the same data, IPCS (2003) concluded that epidemiological studies suggested PCB exposure-related increases in cancers of the digestive system, notably the liver, and of malignant melanoma. Due to limitations of the studies, the data were considered insufficient for a clear identification of exposure-response relationships. It was stated that no consistent picture emerged for any cancer site, that many studies were limited by the small numbers of observed deaths and incomplete exposure assessments, and that confounding exposures were present in some studies (188).

In 2005, NTP concluded that several mixtures of PCBs were reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity in experimental animals (284). The conclusion was mainly based on the IARC evaluations.

Selected studies/reviews

The most important cohort mortality studies reported by ATSDR with focus on the cancers primarily considered related to PCBs are described below. Later studies of occupationally exposed workers, e.g. follow-up studies of these cohorts, are also included. Studies of the general population examining associations between serum or adipose tissue levels of PCBs and occurrence of cancers, mainly those cancer diseases discussed in the recent literature in connection with PCBs, are also described. Due to the large number of studies reporting on breast cancer, principally reviews were used to describe current knowledge.

One of the studies (33) examined by ATSDR was a retrospective cancer mortality study of 544 male and 1 556 female workers employed in the manufacture of PCB-impregnated capacitors at an Italian plant for ≥ 1 week during 1946–1978 and followed through 1982. Three measurements (Aroclor 1254) from 1954 showed air

PCB concentrations of 5 200–6 800 μg/m^3, whereas in 1977, concentrations (Pyralene 3010) were 48–275 μg/m^3. In 1977 and 1982, mean concentrations of PCBs (Aroclor 1254) in blood were 283 and 203 μg/l, respectively. In men, the mortality (SMR, 95 % CI) from all cancers (1.8, 1.04–3.0) and from cancer of the digestive tract (2.7, 1.1–5.7) (6 cases: 1 liver, 1 biliary tract, 2 pancreas, 2 stomach) were significantly elevated. In women, the mortality from malignant tumours (2.3, 1.2–3.8) and from haematological cancer (3.8, 1.1–8.8) was significantly higher than expected. In a subsequent study adding 9 years of follow-up, none of the excess mortalities remained significant, but mortality from digestive system cancers was still increased (SMR 2.0, 0.9–3.6). Among the limitations of the two studies were questionable grouping of digestive system cancers (19, 188).

Two cases of liver and bile duct cancer were observed (0.78 expected, standard incidence ratio (SIR) 2.6, 95 % CI 0.3–9.3) in a small retrospective cohort study of male workers (n = 242) employed for at least 6 months between 1965 and 1978 at a Swedish capacitor manufacturing facility and followed up through 1991. The workers were exposed to PCBs by air, but also dermal exposure was common. The airborne PCB level measured at one occasion was 100 μg/m^3 (146).

A retrospective study of 887 male and 874 female *Yusho* victims demonstrated significantly increased mortality from liver cancer in males, but not in females. However, there was no significant increase in one of two locations, and the cancer could not be conclusively associated with *Yusho* exposure. No significantly increased mortality from cancer of the liver and intrahepatic bile ducts was found in a retrospective mortality study of 1 940 *Yu-Cheng* cases. In the latter cohort, an increase in mortality from Hodgkin's disease was reported in the males (19).

Another study examined by ATSDR was a large retrospective cohort mortality study of 138 905 male electrical utility workers in five companies, employed at power plants for at least 6 months between 1950 and 1986 (250). The degree of exposure to insulating fluids containing PCBs during the average working week was estimated by industrial hygienists, safety personnel etc. Overall cancer mortality and mortality from cancer of the liver or brain were not related to cumulative exposure to dielectric fluids containing PCBs. Significant increases in mortality from malignant melanoma were reported for the mid- and high-cumulative exposure groups, lagging exposure by 20 years. Risk ratios (RRs) were 2.6 (95 % CI 1.1–6.0) and 4.8 (1.5–15), respectively, for cumulative exposures of 2 000–10 000 hours and > 10 000 hours. The study is limited by small numbers of subjects in the groups with higher exposure and longer latency and possibly by incomplete control of confounding due to exposure to sunlight (19, 188).

In an update through 1998 of an Indiana capacitor-manufacturing cohort (n = 3 569 of which 852 women) exposed to PCBs from 1957 to 1977, an excess in mortality (SMR, 95 % CI) from malignant melanoma (2.4, 1.1–4.6, 9 deaths) and possibly from brain cancer (1.9, 1.0–3.3, 12 deaths; if omitting 2 possible metastases 1.6, 0.8–2.9) was reported (321). However, melanoma mortality was not associated with estimated cumulative PCB exposure, and brain cancer mortality did not demonstrate a clear dose-response relationship with estimated cumulative PCB exposure. Other cancers of *a priori* interest (e.g. in rectum, biliary passages, liver and gallbladder) were not in excess, nor was breast cancer (in men and women

combined). PCBs, mainly di- to tetrachlorobiphenyls, were used as dielectric fluid and sometimes there was extensive dermal contact. Serum from 221 Indiana workers was collected in 1977 and mean PCB levels of 546 and 111 µg/l serum for the most and least exposed workers, respectively, were reported (321).

A recent case-control study included 80 cases of malignant melanoma (patients from the general population) and 309 control subjects. Life-time sun exposure information, data on pigmentation variables and sun sensitivity data were collected along with a blood sample. Concentrations of organochlorine compounds including 14 PCBs were measured in plasma (six PCBs were later excluded). Strong associations were seen between risk of malignant melanoma and plasma levels of the sum of the non-dioxin-like PCBs (adjusted OR 7.0, 95 % CI 2.3–21 for highest vs. lowest quartile, and p for trend < 0.001) or several individual PCB congeners. The strongest association was observed for PCB 187 with an OR of 11.5 (95 % CI 3.3–40) and p for trend < 0.001. The OR for the dioxin-like congeners (PCBs 118 and 156) was 2.8 (95 % CI 1.01–8.0) and p for trend was 0.003. Positive associations were also seen for some organochlorine pesticides. Plasma levels in the highest quartiles were > 192 ng/g lipid for the group of non-dioxin-like PCBs and > 23 ng/g lipid for the sum of the two dioxin-like PCBs. According to the authors, the study had good control for sun exposure, sun sensitivity and phenotypic characteristics known to affect risk of melanoma, but the results need to be confirmed in larger investigations (126).

A retrospective update through 1982 of mortality in a cohort (n = 2 588, initially studied through 1975) of workers at two electrical capacitor manufacturing plants, employed for at least 3 months and considered highly exposed to PCBs (Aroclors 1254, 1242, 1016) between 1940 and 1976, was published in 1987. Personal TWA air samples of Aroclor 1016 were 24–1 260 µg/m^3 in 1977, but the levels had probably been higher earlier. A small excess risk of liver-related cancers was seen, but by excluding one of the liver cancers that was not a primary carcinoma the SMR lost statistical significance (19, 301). In a later study, mortality was updated through 1998 for 2 572 workers. The SMR was 1.2 (95 % CI 1.0–1.4, 157 deaths) for cancer mortality in the update time period. Six new "liver cancers" were observed. Mortality from cancers of the biliary passages, liver and gall bladder (referred to as "liver cancer") was significantly elevated in the cohort for the period 1940-1998 (SMR 2.1, 95 % CI 1.05–3.8, 11 deaths). The SMRs for men and women were 1.9 (0.5–4.8, 4 deaths) and 2.3 (0.9–4.7, 7 deaths), respectively. Elevations in mortality from "liver cancer" did not increase with duration of employment. Further, among women, mortality from intestinal cancer (excluding rectum, ICD-9 code 152-153) was elevated (SMR 1.9, 95 % CI 1.2–2.8, 24 deaths), but did not increase with duration of employment. The SMR for NHL (men and women) was 1.3 (95% CI 0.6–2.4) and 9 of 10 deaths occurred in one of two plants. The highest NHL mortality was observed among workers with less than 10 years of employment (7 deaths). The SMR for prostate cancer was 1.1 (95% CI 0.5–2.4). Six of the seven deaths occurred in workers with 10 years or more of employment (SMR 1.6, 95% CI 0.6–3.4) (300).

When the above mentioned cohort (19, 300) was expanded to include all workers with at least 90 days of potential PCB exposure during 1939–1977 (n = 14 458)

mortality was not elevated for liver-related cancer (biliary passages, liver, gall-bladder) overall, but increased with cumulative exposure (p for trend 0.071). Among women, intestinal cancer (excluding rectum, ICD-9 code 152-153) mortality was elevated (SMR 1.3, 95 % CI 1.02–1.7, 67 deaths), especially in higher cumulative exposure categories, but without a clear trend. Among men, stomach cancer mortality was non-significantly elevated (SMR 1.5, 95 % CI 0.98–2.3, 24 deaths) and increased with cumulative exposure (p for trend 0.039). Mortality from NHL, malignant melanoma, rectal, breast and brain cancers was neither in excess nor associated with cumulative exposure. For malignant melanoma, the SMR was 1.3 (95 % CI 0.8–2.0, 19 deaths) for male and female workers combined and 1.7 (0.9–2.8, 14 deaths) for male workers only. Mortality from multiple myeloma was significantly increased (SMR 1.8, 95 % CI 1.2–2.7, 28 deaths) in workers of both sexes (combined) in the total cohort, but was primarily elevated among men and in one of two plants. Prostate cancer mortality was not elevated (SMR 1.0, 95 % CI 0.7–1.4, 34 deaths), but increased with cumulative exposure (p for trend 0.0001). RRs were calculated for three higher exposure categories relative to the lowest. Significantly increased RRs for prostate cancer were seen in the highest exposure category with no lag and in the two highest categories with a 10- or 20-year lag. The RR was 5.2 (95 % CI 1.7–16) for the second highest and 10.3 (3.5–31) for the highest category at a 20-year lag. According to the authors, this was the first occupational cohort study showing a strong exposure-response relationship between cumulative PCB exposure and mortality from prostate cancer. The workers were typically exposed to PCBs both dermally and by inhalation (19, 301).

Suggestive evidence of an association between PCBs and prostate cancer mortality was seen in a nested case-control study (387 cases, 5 controls for each case) based on a cohort of 138 905 men who were employees of five US electric utility companies between 1950 and 1986. The OR for prostate cancer mortality among those with the highest cumulative PCB exposure (36 cases, 109 controls) was 1.5 (95 % CI 0.97–2.2) after adjustment for suspected confounding factors (61).

Groups of PCBs were investigated in a hospital-based case-control pilot study of 58 prostate cancer cases and 99 controls. Serum samples were analysed for a total of 30 PCBs. In multivariate analyses, the ORs of prostate cancer among men with the highest concentrations ($\geq$ 0.49 µg/l) of moderately chlorinated PCBs or PCBs that were phenobarbital-type inducers were about 2.4 (significant only as non-lipid-adjusted OR) compared to men with the lowest concentrations ($\leq$ 0.23 µg/l). Moreover, based on a test for trend, the risk of prostate cancer tended to increase with increasing concentrations. Dioxin-like PCB congeners were not found to be associated with prostate cancer (315).

In a case-control study, Hardell *et al* reported an association between adipose tissue concentrations of certain POPs and prostate cancer, significantly so e.g. for enzyme-inducing PCBs and lower chlorinated PCBs at prostate specific antigen (PSA) > 16.5 ng/ml (154). The ORs for PCB 153 were 30 (95 % CI 3.2–284, 28 cases, 10 controls) in cases with PSA > 16.5 ng/ml and 7.9 (2.0–31) in cases with PSA > 10 ng/ml. However, the findings must be interpreted with caution, since the confidence intervals were wide (154).

The association between plasma organochlorine level and prostate cancer was investigated in a nested-case control study within a large prospective cohort study of 14 203 men 40–69 years old followed from 1990 to 2005 (mean follow-up period of 12.8 years). In total, 201 participants with newly diagnosed prostate cancer were matched with 402 controls. Associations were analysed for total PCBs, 41 individual PCBs, PCB groupings according to Wolff *et al* (see Section 9.2), as well as for many other organochlorine compounds. Median plasma levels of total PCBs were 425 and 448 ng/g lipid among cases and controls, respectively. No significant increase in total prostate cancer was seen for any organochlorine compound. Total PCBs in plasma was inversely associated with advanced prostate cancer but without statistical significance. The authors concluded that the results suggested that exposure to organochlorines is not associated with prostate cancer in general populations (333).

Similarly, a recent case-control study with 79 incident prostate cancer cases and 329 matched controls indicated that long-term low-level exposure to organochlorine pesticides and PCBs in the general population does not contribute to increased prostate cancer risk. Seven pesticides and nine PCBs (PCBs 99, 118, 138, 153, 156, 170, 180, 183 and 187) were measured in plasma and included in the risk analysis (separately and for PCBs also as a group). The geometric mean of total PCBs in plasma was 572 and 640 ng/g lipid in cases and controls, respectively (17).

The risk of NHL in subjects with occupational exposure to solvents, metals, organic dust and PCBs was investigated in an Australian study (694 incident cases, 694 controls). Exposure to PCBs did not seem to increase the risk of NHL overall (OR 1.1, 95% CI 0.5–2.4), but only 25 subjects were considered exposed to PCBs. Those judged to have "possible" exposure to PCBs had lower risk of NHL than those with "probable" exposure. ORs for those with possible and probable exposure were 0.4 (95% CI 0.1–1.3) and 4.5 (0.97–21), respectively. Yet, no significant dose-response relationships were seen for PCBs when level, years or frequency were used as metrics of exposure. However, occupational exposure to solvents seemed to be associated with NHL (124).

A nested case-control study (74 cases, 147 matched controls), part of a prospective US study, showed a strong dose-response relationship between prediagnostic serum PCB concentrations and risk of NHL. Twenty-eight PCBs and DDT were among the measured compounds in serum. Median concentrations of PCBs in serum were 951 ng/g lipid in patients and 864 ng/g lipid among referents. Matched ORs (95% CI) of developing NHL (2^{nd} to 4^{th} quartile compared to 1^{st} quartile) were 1.3 (0.5–3.3), 2.8 (1.1–7.6) and 4.5 (1.7–12), respectively (p for trend 0.0008). Serum DDT concentrations were not associated with risk of NHL. There was evidence suggesting that seropositivity for the Epstein-Barr virus early antigen potentiated the effects of serum PCBs. The authors concluded that the results should be regarded as hypothesis-generating and required replication (319).

According to Carpenter (57), a later report from the same group did not find a relation between NHL and any of nine other measured chlorinated pesticides.

A study focusing on specific PCB congeners (102) examined lipid-corrected PCB concentrations in prospectively collected serum or plasma from NHL cases

and controls in three cohorts (nested case-control studies), one cohort from Norway and two cohorts from the US (including the one mentioned above in Rothman *et al* (319)). The number of participants in the three cohorts were 190 cases and 190 controls (Janus, Norway), 74 cases and 147 controls (CLUE 1, US), and 30 cases and 78 controls (Nurses' Health Study, US), respectively. All blood samples were collected in the 1970s or 1980s and 36, 28 and 21 PCB congeners, respectively, were measured in serum/plasma (concentrations of 36, 7 and 18 PCBs, respectively, were above the limit of detection in at least 50 % of subjects). Particular focus was on PCBs 118, 138 and 153, which were moderately to highly correlated with each other. There were exposure-response trends for all three PCBs (and for total PCBs) with risk of NHL in all three cohorts, especially among subjects diagnosed closer to the date of blood collection. DDE slightly to moderately confounded the PCB associations. In the two larger cohorts, serum concentrations were categorised into quartiles of the distributions and stratified analyses were done for the subgroups with shorter follow-up periods ($\leq$ 16 years and $\leq$ 12 years, respectively). In these subgroups, adjusted ORs (95 % CI) for the risk of NHL for highest versus lowest quartiles of PCB 118 were 5.3 (1.5–19) with p for trend < 0.005 and 13 (1.6–107) with p for trend < 0.05. In the smallest cohort, the maximum follow-up period was 5 years, and when exposure to PCB 118 was divided into tertiles, the adjusted OR (95 % CI) for the highest tertile compared to the lowest was 3.3 (0.9–12) and p for trend < 0.05. In the three cohorts, the corresponding ORs (95 % CI) for PCB 138 were 2.5 (0.9–7.1) (p for trend < 0.005), 7.8 (1.8–34.6) (p for trend < 0.005) and 3.8 (1.1–13) (p for trend < 0.05), and for PCB 153 3.6 (1.3–9.9) (p for trend < 0.005), 2.7 (0.7–9.8) (p for trend < 0.05) and 3.2 (0.9–11.8) (p for trend not given). Similarly, the ORs for total PCBs were 2.9 (1.0–8.2) (p for trend < 0.05), 14.2 (2.2–91) (p for trend < 0.005) and 4.7 (1.2–19) (p for trend < 0.05). Also, many other congeners, e.g. PCB 180, had exposure-response trends in one or two of the three cohorts. The medians of the highest and lowest quartiles for total PCBs in serum were 2 148 and 1 048 ng/g lipid (Janus) and 1 377 and 551 ng/g lipid (CLUE 1) (102).

In a population-based case-control study, 40 PCBs, 7 dioxins, 10 furans and 13 pesticides or pesticide metabolites were measured in plasma of 100 untreated NHL cases and 100 control subjects (only 15 PCBs were included in the risk analyses). Significant exposure-response trends for an increased risk of NHL were reported for PCBs 156, 180 and 194. ORs (95 % CI) for highest quartiles versus lowest quartiles were 2.7 (0.97–7.5) (p for trend 0.03) for PCB 156, 3.5 (1.3–9.1) (p for trend 0.01) for PCB 180, and 2.7 (1.04–6.9) (p for trend 0.04) for PCB 194. Analyses of levels above the 95th percentile showed slightly stronger associations for PCBs 180 and 194, but not PCB 156. No significant elevations of ORs or exposure-response trends for increased risk of NHL were seen e.g. for PCBs 118, 138/158 or 153. Total PCBs (non-coplanar PCBs) were associated with a non-significant, increased NHL risk (OR 1.8, 95 % CI 0.7–5.1) for highest versus lowest quartile (p for trend 0.24). Corresponding ORs (95 % CI) for PCB TEQs and total TEQs were 1.5 (0.6–3.7) and 2.2 (0.8–6.2), respectively. Several furans were positively associated with NHL (87).

Plasma levels of dioxin-like PCBs 118 and 156 were significantly associated with increased risk of NHL with an OR of 1.8 for the highest versus lowest quartile in a Canadian population-based case-control study. Dioxin-like PCBs summed had an OR of 1.8 (95% CI 1.02–3.2) after adjustment for oxychlordane, although without a significant trend (p = 0.06). Some non-dioxin-like PCBs (PCBs 153, 170, 180, 187) also showed significant associations. The PCB congener with the strongest association was PCB 180 (OR 1.9, 95 % CI 1.2–3.1). The OR for non-dioxin-like PCBs summed was 1.6 (95 % CI 0.9–2.7) (p for trend 0.045) after adjustment for oxychlordane. In total, the study comprised 422 NHL cases and 460 control subjects. The measured organochlorines included 14 PCBs, but only 11 were included in the analyses. The sum of total PCBs in the highest quartile was > 220–6 571 ng/g lipid (369).

In a prospective study, 205 NHL cases diagnosed 1982–2003 were compared to 409 matched control subject. DDE and PCB concentrations were measured in plasma samples collected in the early 1980s (14 916 men provided a blood sample). In total, 51 PCB congeners were assayed. Concentrations of PCBs were categorised in quintiles based on the distribution among controls and the lowest quintile was used as reference category. The risk of NHL was positively associated with the sum of 51 PCB congeners, the group of immunotoxic congeners (PCBs 66, 74, 105, 118, 156 and 167), the individual PCB congeners 118, 138, 153 and 180, and the sum of the last four congeners. The simple OR for the highest versus lowest quintile for the sum of all PCBs was 1.9 (95 % CI 1.1–3.2, p for trend 0.001), with similar trends for individual congeners and groups. The median concentration for the sum of all PCBs in the highest quintile was 1 385 ng/g lipid (range > 1 121–5 322) vs. 518 ng/g lipid (163–617) in the reference category. No association between DDE and NHL was observed. A comparison of the major NHL histologic subtypes and PCB exposure (across tertiles) indicated that the associations were somewhat stronger for the diffuse large B cell lymphoma and follicular lymphoma subtypes than for chronic lymphocytic leukaemia/small lymphocytic lymphoma (34).

In a similarly performed study, no consistent evidence of an association between PCBs (total, immunotoxic or individual) and the risk of NHL was found. This case-control study (145 NHL cases, 290 controls) was nested within the Nurses' Health Study, a prospective cohort of US women. The median time to diagnosis for cases was 5.8 years. Women with a diagnosis of NHL before or within 6 months of blood collection and those with a prior diagnosis of cancer (other than non-melanoma skin cancer) were excluded. Median plasma levels for the sum of 51 PCBs were 945 and 407 ng/g lipid in the highest and lowest quartiles, respectively (quartiles based on the distribution among controls) (218).

In a recent Swedish study of 99 cases with NHL and 99 population based controls, plasma concentrations of organohalogen compounds (including 35 PCBs) were measured. Median concentrations in the controls were used as cut-off. In the group with a sum of PCBs above the control median, the OR was 2.0 (95 % CI 0.99–3.9) for total NHL. For follicular NHL, significantly increased ORs were seen in groups with sum of PCBs (OR 5.9, 95 % CI 1.5–24), moderately chlorinated PCBs (5.8, 1.5–23) and highly chlorinated PCBs (9.6, 1.9–49) above the cut-offs.

An interaction with titres of antibodies to Epstein-Barr virus early antigen (IgG) was found. Increased ORs for total NHL and diffuse large cell NHL were observed in the groups with IgG > 40 (control median) combined with values predominantly above cut-offs for sum of PCBs, low-, moderately- or high-chlorinated PCBs, or "immunotoxic PCBs" (153).

No evidence of an association between NHL risk and plasma levels of PCBs and organochlorine pesticides was found in a retrospective study in which nine PCB congeners (PCBs 28, 52, 101, 118, 138, 153, 170, 180, 194) and 17 organochlorine pesticides were measured in plasma samples of 174 NHL cases and 203 controls from France, Germany and Spain. Total PCBs, individual PCBs as well as functional PCB groups did not show an association with NHL or common subtypes, namely diffuse large B cell lymphoma or chronic lymphocytic leukaemia/small lymphocytic lymphoma, in the overall study population. When the Spanish study group alone was considered, the lack of an association with "immunotoxic PCBs (PCBs 138, 153, 180)" was confirmed with an OR for diffuse large B cell lymphoma of 0.7 (95 % CI 0.3–1.6) for plasma levels above the median, whereas the French and German subgroups combined had an OR of 3.2 (0.9–11.5) for plasma levels above the median and an OR of 6.1 (1.0–37.8) in the upper quartile. Half of the Spanish samples were taken after cytostatic treatment had been initiated. According to the authors, possible reasons for the heterogeneity included metabolic interference by elevated blood concentrations of competing organochlorine pesticides and other PCBs, interaction with viruses and other pathogens, and genetic polymorphism (71).

Colt *et al* showed that the relation between PCB 180 or TEQs in plasma and NHL risk may be modified by particular variants in immune genes. Thus, the associations were limited to certain genotypes. The results suggested that interferon-γ and IL-4 broadly affected the relation between organochlorine exposure and NHL risk, whereas the effects of IL-8, IL-10 and IL-16 appeared to be limited to PCB 180. Still, the results require replication in additional large studies and in pooled analysis (75).

Regarding breast cancer risk among occupationally exposed, a review from 2003 concluded that no increased risk for breast cancer had been found in retrospective cohort studies of workers exposed to PCBs (40). However, in a recent study, an increased risk of breast cancer among non-white female workers was suggested. In this study, 5 752 women employed for at least 1 year at any of three capacitor plants were followed through 1998. The overall exposure period for the cohort ranged from 1939 to 1977. In a sub-cohort of workers with complete questionnaire data regarding e.g. smoking, age at first live birth, breast cancer in female relative, and hormone use, the number of breast cancer cases by race were 131 (white) and 14 (non-white). Among non-white women, the effects of increasing exposure were positive and statistically significant, whereas among white women, cumulative exposure and duration of exposure had little effect on breast cancer risk. Yet, the small number of non-white cases limits interpretation of the findings (360).

In the general population, epidemiological evidence does not support the hypothesis of an association between environmental exposure to PCBs in adulthood

and risk of breast cancer, although uncertainties remain for individual PCB congeners (e.g. oestrogenic short-lived PCB congeners) or selected subgroups of women. The vast majority of prospective and retrospective studies did not find any association between total PCB concentrations in serum, plasma or breast adipose tissue and breast cancer risk. A few studies have suggested that higher levels of PCBs possibly are related to increased risk of breast cancer recurrence or decreased survival (19, 47, 275, 325).

The potential association between organochlorine exposure and breast cancer was investigated e.g. in the case-control study by Ward *et al* (2000). A total of 150 controls were matched to 150 randomly selected cases by date of birth and date of sample collection, and stored pre-diagnostic sera from 1973 through 1990 from the Janus serum bank in Norway was used. Mean serum concentrations in cases and controls were compared for 26 PCB congeners with > 90 % of samples above the detection limits. Comparison was made for total PCBs and individual congeners, and the congeners were also grouped as proposed by Wolff *et al* (Section 9.2) (no PCBs in group 1A). No significant positive associations for PCBs with breast cancer risk were shown. Total PCB mean serum concentrations were 4.8 and 5.1 µg/l (776 and 807 ng/g lipid) in cases and controls, respectively (408).

In recent years, a number of studies have investigated the influence of various genetic polymorphisms on the association between PCB levels and breast cancer risk. The most consistent evidence for a modifying effect of a polymorphism is for the *CYP1A1* gene. Some studies have shown a higher breast cancer risk associated with higher PCB exposures among postmenopausal white women with the *CYP1A1-m2* genetic variant (also referred to as *CYP1A1*2B*) (47, 134).

11.4 Reproductive and developmental effects

There are several studies concerning pregnancy outcome and other reproductive parameters in relation to PCB exposure, and the literature regarding, prenatal and/or early life exposure to PCBs and effects on the foetus, child and young (or adult) is extensive. Some important studies and reviews are described in the sections below. For a more complete survey of this literature the reader is referred to reviews by e.g. Bonde *et al* (2008), Boucher *et al* (2009), Schantz *et al* (2003) and Wigle *et al* (2008) (38, 41, 341, 420).

11.4.1 Fertility and related effects

11.4.1.1 Fertility and related effects: Men

Occupational studies provide no clear indications of PCB-related reproductive effects in men. However, more recent epidemiological data on the general population suggest an inverse association between PCB levels and sperm motility, although no major impact on fertility has been shown (38, 158). In a review, Meeker and Hauser (2010) concluded that the associations on sperm motility were generally consistent across studies in different countries. The PCB exposure in these studies ranged from low to high "background" levels, the latter resulting from consumption of contaminated fish, and to even higher "exposure" levels due to ingestion of contaminated rice oil. It was also stated that associations across studies were

fairly consistent with regard to an inverse association between PCBs and serum testosterone, though details of the findings varied (total testosterone, free or bound fractions) (269). Alternative explanations are possible, e.g. simultaneous exposures to other classes of chemicals with effects on male reproductive parameters (38, 158, 269). Effects of PCBs on sperm counts are not generally supported by published data, but results from a recent study suggest that men with specific polymorphisms in the androgen receptor gene might be more vulnerable (38, 325).

In a study of transformer repair workers currently and previously exposed to PCBs from air and contaminated surfaces (predominantly Aroclor 1260), no difference in sperm counts was found between the 38 investigated subjects and 31 unexposed workers, and no significant correlation with PCB concentration was seen. Eight-hour TWA concentrations of PCBs were 0.01–24 μg/m^3 (sample concentrations up to 60 μg/m^3) (100, 101). The measured total serum median values as reported in a later study (27 PCB peaks were quantified) were approximately 43 μg/l for currently exposed workers, 30 μg/l for formerly exposed workers and 13 μg/l for controls (114).

An overview of the main results that emerged from INUENDO, a large-scale population-based epidemiological study evaluating xenobiotics as causes of subfertility and other reproductive disorders (18 published core papers), was given by Bonde *et al* (38). The INUENDO studies combine four interview studies of time to pregnancy with four cross-sectional studies of male reproductive hormones and semen quality. Three study populations (Greenland, Warzaw, Poland and Kharkiv, Ukraine) included pregnant women and their male spouses. The fourth study population included Swedish fishermen and fishermen's wives. Blood samples (PCB 153, DDE) were obtained from 1 992 women and 1 172 men. The integrated xenohormone (oestrogen receptor and androgen receptor) and dioxin-like (Ah receptor) activities in serum were evaluated by the CALUX assays and 5 male reproductive hormones in serum were measured. In addition, conventional semen characteristics were studied (participation rates 7–79 %, approximately 200 men at each site). The CALUX activities were only weakly correlated with PCB 153 and DDE, indicating that these organochlorines are not the important contributors to the measured xenobiotic serum activity. Across all study populations, none of the male reproductive hormone levels varied consistently with the serum concentrations of PCB 153 (Table 16). Yet, in some (but not all) regions, several endocrine responses were associated with PCB 153 blood levels. The median serum concentrations of PCB 153, as well as, DDE varied more than 10-fold between regions (38).

Bonde *et al* (38) reported that progressive sperm motility was inversely related to serum PCB 153 levels among both Inuits and Europeans with consistent indications of exposure response relationships (Table 16). Sperm count and the proportion of morphologically normal sperm was not related to PCB 153 in any study group. However, among the subset of men with short androgen receptor polyglutamine-encoding (CAG) repeat length, which makes up about one-fifth of the entire study population, high levels of PCB 153 were significantly related to low sperm counts. None of several seminal markers of epididymal and accessory sexual gland function varied consistently with PCB 153 serum levels across all regions. Damage of sperm

Table 16. Adjusted geometric mean values of male reproductive hormones in serum, semen characteristics and markers of epididymal and accessory sex gland function by categories of PCB 153 in serum (extracted from Bonde *et al* (38)).

Male reproductive characteristics	Inuits			Europeans		
	Serum PCB 153 (ng/g lipid)			Serum PCB 153 (ng/g lipid)		
	0–50	51–200	>200	0–50	51–200	>200
No. of semen samples	10	8	104	300	182	87
No. of blood samples	19	150	145	256	183	91
Male reproductive hormones						
Follicle-stimulating hormone (IU/L)	4.2	4.1	4.5	3.9	4.3	4.8
Luteinising hormone (IU/l)	3.1	3.9 [a]	4.1 [a]	3.7	4.0	3.7
Inhibin B (ng/l)	160	170	182	184	182	165
Sex hormone-binding globulin (mmol/l)	28	29	29	25	31 [a]	32 [a]
Free testosterone	1.63	1.73	1.75	1.87	1.68 [a]	1.65 [a]
Conventional semen characteristics						
Volume (ml)	4.3	3.4	3.0 [a]	3.1	3.6	3.3
Concentration (million/ml)	58	52	53	46	53	64
Count (million)	229	274	149	142	185	200
Normal sperm (%)	8.0	5.9	5.9	6.2	5.8	5.3
Progressive sperm (%)	65	57	53 [a]	60	57	51 [a]
Sperm chromatin integrity						
DNA fraction index (%DFI)	8.0	7.6	7.5	9.9	12.8 [a]	15.4 [a]
High DNA stainability (%HDS)	6.6	12.6 [a]	11.0 [a]	9.0	9.3	8.9
DNA fraction index (TUNEL (%)	3.5	3.2	2.6	7.7	10.7 [a]	12.0 [a]
Apoptotic markers						
Fas positivity (%)	22.3	16.6	17.6	17.3	16.3	21.6
Bcl-xL positivity (%)	12.7	12.6	10.3	16.6	16.6	20.6
Epididymal and accessory sex gland function						
Neutral α-glucosidase (mU/ejaculate)	25.0	16.6 [a]	15.7 [a]	18.5	26.8 [a]	24.8 [a]
Prostate specific antigen (µg/ejaculate)	8.6	8.0 [a]	8.0 [a]	7.9	8.1 [a]	7.9
Zinc (µmol/ejaculate)	6.6	4.8	4.2	4.5	5.9	5.1
Fructose (µmol/ejaculate)	71	43	44	38	44	35

[a] p-value < 0.05 (exposed versus reference group with PCB 153: 0-50 ng/g lipid).
TUNEL: terminal deosynucleotidyl transferase dUTP nick end-labelling.

chromatin integrity was considerably less frequent in Inuits compared to that in European groups, and only in the latter was impairment of sperm chromatin integrity related to PCB 153 levels (see also Section 11.2). Despite all these effects, fertility in terms of time to pregnancy was not related to PCB 153 except in Inuits for which this finding was of borderline significance and without obvious exposure-response relationship. Also, there was a strong correlation between PCB 153 and DDE among Inuits and it has been suggested that the effect is most likely caused by DDE (see Axmon *et al* (23)).

In an early study on PCBs and semen quality in the general population, analysis of the data by fertility status indicated that the seminal concentrations of PCBs 118, 137 and 153 were inversely correlated with sperm motility in the subset of infertile men (19). Pines *et al* (1987) reported significantly higher blood levels of tetra- and penta- but not hexachlorobiphenyls or total PCBs in infertile males compared to the control population (19). However, levels of DDT and other organochlorine compounds were also increased and because of these and other limitations in the two studies, possible effects on sperm counts and motility could not be solely attributed to PCB exposure (188).

In a study on 305 Swedish adolescent military conscripts (18–21 years), a weak but significant inverse correlation between PCB 153 in serum and the percentage of motile sperm cells assessed by computer-aided sperm motility analyser (CASA) was observed. An increase in PCB 153 levels by 10 ng/g lipid corresponded to 1 % decrease in the analysis. No such effect was seen for sperm concentration or total sperm count. Also, a reduced androgenic activity was implied (weak negative effect on free testosterone levels due to a positive correlation between PCB 153 and sexual hormone-binding globulin levels). The median PCB 153 level in serum was 65 ng/g lipid (309).

In a study on 195 Swedish fishermen with a median PCB 153 serum level of 193 ng/g lipid, the subjects in the highest quintile (range 329–1 460 ng/g lipid) tended to have a decrease in sperm motility compared to subjects in the lowest quintile (39–112 ng/g lipid), although not formally significant. Age-adjusted data for associations between PCB 153 and sperm concentration, total sperm count or hormone parameters were not significant. Neither were there any significant associations between DDE and reproductive hormones or semen characteristics in adjusted data (313). In a concomitant study, no associations between methyl mercury exposure and semen quality or quantity or synergistic effects between methyl mercury and PCB 153 were seen among Swedish fishermen (310).

In a US study of men recruited from infertility clinics (n = 212), associations between semen parameters and 3 individual congeners (PCBs 118, 138 and 153) as well as the sum of 57 PCBs were explored. In addition, an analysis of the relationship between semen parameters and groupings of PCBs, as proposed by Wolff *et al* (see Section 9.2), was conducted. There were significant inverse dose-response relationships in the adjusted analyses (ORs (95 % CI) per tertile) between PCB 138 and sperm motility (ORs 1.7 (0.8–3.4) and 2.4 (1.1–5.0) with p for trend 0.03) as well as sperm morphology (ORs 1.4 (0.6–3.2) and 2.5 (1.06–6.0) with p for trend 0.04). Also, there were inverse, although non-significant, relationships between the sum of PCBs and Group 3 PCBs (phenobarbital *CYP1A* and *CYP2B* inducers) with sperm motility and sperm morphology and weak evidence (non-significant) of an inverse association between DDE and sperm motility. The geometric mean levels of PCBs 118, 138 and 153 and the sum of PCBs in serum were 13, 34, 44 and 226 ng/g lipid (159).

Dallinga *et al* (81) recruited men with very poor semen quality (n = 34) and with normal semen quality (n = 31) from an infertility clinic. Blood concentrations of hexachlorobenzene, DDE, DDT, four PCBs and metabolites were determined. Mean blood concentrations of PCBs 118, 138, 153 and 180, and the sum of PCBs were 0.05, 0.37, 0.41, 0.33 and 1.17 µg/l, respectively. Overall, no relationship between the organochlorine levels and sperm count or progressive and overall motility was observed. Among men with normal semen quality, sperm count and sperm progressive motility were inversely related to the blood concentrations of combined PCB metabolites (81, 158).

Higher percentage of sperm with abnormal morphology and a higher oligospermia rate were seen in a study of 40 men from Taiwan who had ingested contaminated rice oil some 20 years earlier compared to 28 unexposed men. Reduced ability of sperm from exposed men to penetrate the hamster oocyte was reported.

No statistical adjustment for confounders was done, although age and percentage of smokers were similar in both groups (158).

11.4.1.2 Fertility and related effects: Women

Few data regarding fertility in occupationally PCB exposed women are available. In one study, no effect on number of pregnancies was observed in capacitor manufacturing workers (19). Results from studies of reproductive effects in females from the general population (including consumers of contaminated fish) are inconsistent. Regarding menstrual disturbances, it has been concluded lately that it is unlikely that exposure to PCBs in the general population is a main cause, even at relatively high exposure levels (385). Studies of endometriosis do not clearly support or refute the possibility of an association with PCB exposure (160).

As mentioned, very little information is available from the occupational exposure situation. No apparent effect on number of pregnancies was observed in capacitor manufacturing workers exposed to Aroclors 1254, 1242 and/or 1016 for a minimum of 3 months between 1946 and 1975. Evaluation of birth data on 172 high-exposure and 184 low-exposure workers showed no significant differences in the mean number of pregnancies (not adjusted for potential confounders). High-exposure workers were directly exposed to Aroclors for at least 1 year prior to birth. Area air samples collected in 1977 showed geometric mean concentrations of 310 and 27 $\mu g/m^3$ in the high- and low-exposure groups, respectively (19).

An overview of 12 epidemiological studies assessing the relationship between endometriosis and organochlorine exposure was published by Heilier *et al* (160). Serum measurements included some/all dioxin-like PCBs, other dioxin-like compounds and, in eight studies, non-dioxin-like PCBs. Only one of seven studies which took Ah receptor ligands into consideration demonstrated a significantly increased risk to develop deep endometriotic nodules associated with higher serum concentrations of dioxin-like compounds (PCDDs/PCDFs and all dioxin-like PCBs were measured). In a small study in which non-dioxin-like PCBs (marker PCBs) were measured, an OR of 3.1 (95 % CI 1.1–8.9) was reported for deep endometriotic nodules. None of the epidemiological studies demonstrated an association between dioxin-like compounds and peritoneal endometriosis, but one study reported a significant relationship with marker PCBs (PCBs 28, 52, 101, 105, 118, 138, 153, 156, 167, 170 and 180). ORs were 6.5 (95 % CI 1.5–28) for levels of 250–360 ng/g lipid and 5.3 (1.3–23) for levels > 360 ng/g lipid compared to referents (< 250 ng/g lipid) (adjusted by age and smoking habits). According to the authors, the studies did not clearly support or refute a role for organochlorines in the etiopathogenesis of endometriosis. Still, they summarised that the deep nodular form of endometriosis appears to be associated with higher serum levels of both dioxin-like compounds (including PCBs) and marker PCBs (160).

In a large epidemiological study from the US, self-reported menstrual cycle characteristics were assessed in relation to low-level exposure to DDE and PCBs. The mean PCB level in serum in the study population (2 314 pregnant women) was 3.1 µg/l (median 2.7 µg/l, samples collected in the early 1960s). An association between increasing serum levels of total PCBs (11 congeners measured) and somewhat longer menstrual cycles was reported. The difference was 0.7 days in

the highest (≥ 5.0 µg/l) as compared to the lowest (< 1.2 µg/l) exposure group. Adjusted mean cycle length was not associated with DDE levels, and levels of PCB or DDE were not associated with bleeding duration, heavy bleeding or dysmenorrhea (76).

In another study, information on menstrual cycle characteristics were obtained by questionnaires, and PCB and DDE were measured in serum samples from a total of 1 494 women (from Greenland, Poland and Ukraine as well as Swedish fishermen's wives). PCB 153 was used as a biomarker of PCB exposure. No consistent effects of PCB exposure on menstrual cycle characteristics (cycle length, irregularity) were obtained across populations. The risk for short cycles (≤ 24 days) increased markedly in the Swedish population with increasing PCB levels. The estimated PCB (and DDE) exposure in Sweden was higher than in the three other populations, but the differences in menstrual cycle characteristics between countries should be interpreted with caution. Since the observed effects in this study were not consistent, the authors considered it unlikely that PCBs are a main cause of menstrual disturbances, even in populations with relatively high levels of exposure (385).

Findings for reproductive or developmental endpoints from a study of the population-based New York State Angler cohort have been detailed in several reports. Consumption of PCB-contaminated fish was associated with a slightly shorter length of menstrual cycle, but this was a preliminary finding and needs to be interpreted cautiously. No increased risk of conception delay in females was seen when time to pregnancy was used as the outcome measure of conception, but when the outcome measure was probability of conception in exposed versus unexposed during a given menstrual cycle (fecundability ratio), maternal consumption of fish for 3–6 years was associated with a reduction in fecundability. No increased risk for spontaneous foetal death was reported (19).

The ability to become pregnant (time to pregnancy) was examined prospectively in 83 women from the New York State Angler cohort. In total, 76 PCBs were quantified in serum and summed and further divided into three groupings according to Cooke *et al*, i.e. in relation to supposed oestrogenic and antioestrogenic effects (Section 9.2). The concentration of total PCBs was 16.2–32.8 µg/l in the 3rd tertile and 10.6–14.5 µg/l in the 1st tertile. No significant differences in PCB concentrations (in tertiles) were observed by women's ability to become pregnant. However, it was stated that oestrogenic and antioestrogenic PCB concentrations conferred reduced fecundability ORs (longer time to pregnancy) in fully adjusted models (OR 0.3, 95 % CI 0.03–3.9, OR 0.01, 95 % CI < 0.0–2.0), and the group of "other" PCBs increased fecundability OR (OR 1.4, 95 % CI 0.9–2.4) (52).

Time to pregnancy (self-reported estimates) was studied by Law *et al* in 390 pregnant women enrolled at 12 study centres in the US from 1959 to 1965. Maternal serum samples (third trimester serum) were analysed for 11 PCB congeners, DDT and DDE after being frozen for more than 30 years. Evidence suggesting an association between increasing PCB levels and increased time to pregnancy was found when data were adjusted for e.g. DDE, age and smoking. Time to pregnancy increased in the highest (PCBs ≥ 5 µg/l) compared to the lowest (PCBs < 1.2 µg/l) exposure category with a fecundability OR of 0.65 and the same went for DDE.

When expressed on a lipid basis, increased time to pregnancy was attenuated slightly for women with higher serum PCB levels and was no longer associated with higher serum DDE levels. There were no PCB congener-specific associations with time to pregnancy, nor was there an association between DDT and time to pregnancy. The authors concluded that evidence of an association between PCB or DDE exposure and time to pregnancy was weak and inconclusive (225).

No support for an inverse association between plasma concentrations of PCB 153 and time to pregnancy was observed in Swedish east coast fishermen's wives (n = 121) based on retrospectively estimated PCB 153 plasma concentrations at the time immediately preceding pregnancy. The subjects were categorised in a low- (37–206 ng/g lipid), medium- (207–330 ng/g lipid) and high- (331–1 036 ng/g lipid) exposure group. Actual PCB 153 concentrations were available from plasma samples drawn in 1995 (median 144 ng/g lipid) (21). Fishermen's sisters were investigated (n = 165) and these data as well as data for the combined group of fishermen's wives and sisters (n = 286) were presented in a subsequent study (22). The median PCB 153 concentration in serum of the sisters was 115 ng/g lipid and estimated past PCB 153 concentrations in the low-, medium- and high-exposure groups were 45–148, 149–239 and 243–1 111 ng/g lipid, respectively (24–178, 180–267 and 271–1 111 ng/g lipid, respectively, in the combined data set). A decrease in the time to pregnancy for the high-exposure groups was found among the fishermen's sisters and was also present in the combined analysis (sisters and wives). Furthermore, the 16 fishermen's sisters for whom the first planned pregnancy ended in a miscarriage had lower estimated past PCB 153 concentrations than the fishermen's sisters with a live birth. The results were similar when the fishermen's wives were included in the analysis.

In a later study, time to pregnancy and exposure biomarkers in serum (e.g. PCB 153) were obtained for 1 505 women in four cohorts, including 508 Swedish fishermen's wives and women from Greenland, Poland and Ukraine. Exposure biomarkers were also measured in 778 men (not in the Swedish cohort). The Swedish cohort had the highest serum concentrations of PCB 153 (median 150 ng/g lipid, 95 % range 34–530). The main finding of the study was that in the Inuit population there may be a prolonged time to pregnancy associated with serum concentrations of PCB 153 and DDE, mainly for female exposure (still, the Inuit women had shorter time to pregnancy than women from Poland or Ukraine). The data from Sweden and Poland indicated no effect of PCB exposure on time to pregnancy, whereas a similar pattern as for the Inuits was seen for the cohort from Ukraine with respect to PCB 153, despite considerably lower exposure levels. However, the authors reported that previous studies indicated that the effect is most likely from serum concentrations of DDE (23).

Menstrual irregularities (i.e. altered intervals, duration and flow) were observed in women exposed during the *Yusho* poisoning incident, but heating of the PCB-contaminated rice oil also resulted in the formation of other contaminants of concern, e.g. dibenzofurans and ter- and quarterphenyls (19).

11.4.2 Effects in offspring

11.4.2.1 Prenatal and childhood growth, sex ratio

Few studies deal with birth weights of babies born to occupationally PCB exposed women. Epidemiological studies including new-born from women of the general population are conflicting (19, 98), although perinatal exposure to high concentrations of PCBs and structurally-related chemicals, as occurred in *Yusho* and *Yu-Cheng*, affects birth weight and growth during early life (19, 91). It was concluded in the ATSDR review that no firm conclusions can be made regarding growth and development of children and environmental exposures to PCBs. Still, reduced birth weight from *in utero* exposure to some PCB mixtures or groups of congeners could not be excluded, at least at dose levels somewhat higher than those commonly occurring in the general population (19, 170, 274, 328). Further, a relationship between PCB exposure and developmental enamel defects of teeth has been suggested in a few studies on the general population, although the evidence for maternal background PCB exposure was considered inadequate in a recent review (194, 195, 420).

Women workers of two facilities that manufactured capacitors using Aroclors 1242, 1254 and 1016 as their primary dielectric fluid were evaluated in two US studies (383, 384). Birth certificates and hospital/physician records for pregnancies between 1958 and 1975 were used to obtain information on e.g. birth weight and date of the last menses. The high-exposure workers were directly exposed to Aroclors for at least 1 year prior to birth. Infants (n = 51) born to 39 women with high exposure to PCBs had lower mean birth weights and shorter mean gestational ages than infants (n = 337) born to 280 women with low exposure to PCBs. After adjusting for gestational age, the difference in birth weight was markedly reduced. The infants born to high-exposure women were on average lighter than matched community controls, whereas those born to low-exposure women were heavier. However, as stated by the authors, there was no information on some important factors known to influence birth weight, e.g. tobacco use and maternal height (383).

In a follow-up study by Taylor *et al* based on the same cohort, interviews were conducted with 405 women. A significant effect of estimated high-homologue PCB exposure on birth weight (decrease) was seen after adjustment for variables known to influence birth weight, but only in the absence of adjustment for gestational age. For gestational age, a small but significant decrease was also observed with an increase in estimated exposure. A total of 172 live births from pregnancies with direct-exposure and 184 births from pregnancies with indirect exposure were used in the analysis. Environmental monitoring had been performed at the facilities. The TWA of PCBs in personal air samples (n = 31) from workers in direct-exposure jobs in 1977 was 168 µg/m^3 (geometric mean). Dermal contact with PCB occurred to some extent and there was exposure to other chemicals. Exposure statuses in 1979 given as serum PCB concentration (geometric mean) for capacitor workers with direct-exposure jobs (n = 147) were 269 µg/l (low homologues), 33 µg/l (high homologues, as Aroclor 1254) and 302 µg/l (total PCBs). For 18 capacitor workers with indirect-exposure jobs, these figures were 50, 11 and 61 µg/l, respectively (384). Longnecker *et al* (248) stated that a large increase in exposure (20 µg/l high-

homologue PCBs in serum) in the study by Taylor *et al* (384) was associated with a small decrease in birth weight (33 g) and gestational length (1.1 days).

The association between maternal occupational exposure to specific chemical compounds and birth of small-for-gestational-age infants was evaluated in a case-referent study using data from a prospective cohort study of pregnant women in West Germany (1987–1988). No association was found with PCB exposure (12/194 affected and 79/1 668 non-affected infants were considered to have PCB-exposed mothers). Chemical exposure at the current workplace was assessed by a job-exposure matrix and PCB exposure categorised as low (353).

Sagiv *et al* (2007) investigated birth outcomes in relation to cord serum PCB concentrations in 722 infants born 1993–1998. The mothers were residing for the duration of the pregnancy in towns adjacent to a PCB-contaminated harbour in Massachusetts. The sum of 51 PCBs, the sum of PCBs 118, 138, 153 and 180, the TEQs for the sum of 5 dioxin-like congeners (PCBs 105, 118, 156, 167 and 189) and for PCB 118 alone were studied. Weak inverse associations were observed between PCB levels and birth weight. Although imprecise and accompanied by wide CIs, mean birth weight was generally lower for higher quartiles of PCB exposure across each congener grouping when the lowest quartile of exposure was used as referent (sum of 51 PCBs: range 0.07–0.24 μg/l serum in the reference group, ranges 0.24–0.38, 0.38–0.60 and 0.61–18.14 for quartiles 2–4). Weaker associations were detected for birth length and head circumference (328).

Further, Sagiv *et al* reported four previous studies that supported an association between low-level PCB exposure and birth weight. In the Michigan study of mothers who consumed PCB-contaminated fish during 1980–1981, lower birth weight and head circumference were found among infants with maternal serum PCB levels ≥ 3 μg/l as compared to infants with maternal PCB levels < 3 μg/l. Overall, lower birth weight, smaller head circumference and shorter gestational age were positively correlated with total PCBs in cord serum (19, 328). In a Dutch study of births during 1990–1992, it was reported that infants with PCB cord plasma levels of 0.8 μg/l weighed 165 g less than infants with 0.2 μg/l (no association was observed for birth length or head circumference). Similar effects were seen when using maternal plasma PCB levels as the exposure variable. Further, both cord and maternal plasma PCB levels were significantly associated with lower growth rates until 3 months of age in the formula-fed group. However, gender was not included as covariate in any of the linear regression models (19, 188, 328, 429). Also the Child Health and Development Study of births between 1964 and 1967 in the US California San Francisco Bay Area was positive (170) (described below). Another of the mentioned studies was a study of births during 1973–1991 (Michigan anglers). In that study, lower birth weight was seen among those in the highest maternal serum PCB category. Six studies of birth weight *not* supporting an association with PCBs were mentioned by Sagiv *et al* as well. Among these were studies of the North Carolina cohort 1978–1982 and of the US cohort 1959–1965. The latter study by Longnecker *et al* (248) is described below. According to Sagiv *et al* (328), studies that found associations with birth weight generally had greater levels of total PCBs than studies that found no associations with birth

Table 17. Median PCB 153 levels in ten studies (adapted from Longnecker *et al* (249)).

Location of population	Years of specimen collection	Number of specimens [a]	Median (ng/g lipid) [b]
US, 11 cities (CPP)	1959–1965	2 737	140
US, California	1964–1967	399	130
US, North Carolina	1978–1982	872	80
US, Michigan	1980–1981	196	120
The Netherlands, 2 cities	1990–1992	415	100
US, New York	1991–1994	50	40
Germany, Düsseldorf	1993–1995	126	140
US, Massachusetts	1993–1998	160	30
Denmark, Faroe Islands	1994–1995	173	450
Canada, Northern Québec	1995–1998	159	100

[a] Number of specimens on which reported or estimated PCB levels were based.
[b] Data for maternal pregnancy serum (or plasma) or data for maternal milk re-expressed as levels in maternal serum.
CPP: collaborative perinatal project, US: Unites States.

weight, although the studies were not directly comparable because of different congener mixtures, biomarkers and analytical techniques.

To compare exposure levels across 10 different study populations from the general population (including several of the cohorts described in this section), Longnecker *et al* compiled PCB levels as represented by PCB 153 (249) (Table 17). By inspection of these data, no obvious correlation between effects on birth weight and median levels of PCB 153 in the different studies is seen. As an example, the two studies (170, 248) published in 2005 analysing US exposure and birth outcome data from 1960s came to different conclusions despite similar median levels of PCB 153 (130 and 140 ng/g lipid). The study by Longnecker *et al* (248) examined births at 12 US study centres and found maternal serum PCB levels during pregnancy essentially unrelated to preterm birth, birth weight or length of gestation. An association of PCBs with small-for-gestational-age birth was observed, but the results were inconclusive and occurred in the absence of an overall decrease in birth weight. There was no suggestion that congeners differed in their relation to preterm birth or small-for-gestational-age birth (248, 377).

Hertz-Picciotto *et al* investigated women in the US California cohort. This study found higher total *in utero* PCB exposure associated with reduced birth weight, smaller head circumference and reduced weight for gestational age in male infants. An increase from the 10^{th} to 90^{th} percentile of total maternal PCB serum concentration was related to 290 g lower (95 % CI -504 to -76) mean birth weight (adjusted) in males. Smaller head circumference and shorter gestation were present, but merely suggestive in girls. Total PCBs was calculated as the sum of PCBs 105, 110, 118, 137, 138, 153, 170, 180 and 187, and the concentrations were higher than most, but not all, populations under study today. The median levels of total PCBs were 616 (5^{th} and 95^{th} percentiles 378 and 1 115) ng/g lipid (170, 377).

Recently, the same team reported that the RR of a male birth decreased by 33 % comparing women at the 90^{th} percentile of total PCBs to women at the 10^{th} percentile of total PCBs (RR 0.7, 95 % CI 0.5–0.9, p = 0.02) or by approximately 7 %

for each 1 µg/l increase in total PCB concentration. All nine PCB congeners with < 30 % of samples below the limit of quantitation showed the same direction of association. The authors concluded that maternal exposure to PCBs may be detrimental to the success of male sperm or to the survival of male embryos. Findings could be due to contaminants, metabolites or PCBs themselves (171).

Tan *et al* assessed prenatal exposure to POPs (41 PCBs, 7 polybrominated diphenyl ethers, 9 pesticides) by determining umbilical cord blood levels in 41 samples collected in Singapore and compared with quantitative neonatal variables. The median level for total PCBs was 30 ng/g lipid (range 5.7–138). It was indicated that chlordanes and PCBs affected birth weight, length and head circumference inversely, whereas other pesticides exhibited positive effects. The presence of PCBs in cord blood seemed to be related to a lowered Apgar score at 1 minute post-birth. Presence of inorganic lead and organic mercury was not investigated (381).

A US study investigating prenatal exposure to PCBs and height and weight in children (n = 150) born 1959–1962 showed that maternal PCB levels were associated with reduced weight among girls, but not among boys. A doubling of maternal levels of mono-*ortho*-substituted PCBs was associated with an 11 % reduction in weight measured at 4 and 7 years. The magnitude of association was slightly less for PCBs with greater degrees of *ortho*-substitution. The results of the analyses using height as the outcome were more equivocal and had a much smaller magnitude of association than that seen for the weight analyses. Results of 21 congeners (PCBs 15, 28, 56, 66, 74, 99, 101, 105, 118, 138, 146, 153, 156, 167, 170, 174, 180, 183, 187, 199, 203) measured in serum during pregnancy were used. The mean level of all PCBs in maternal serum was 9.2 µg/l (219).

In a prospective study by Murphy *et al,* serum samples were collected from 99 women (from a larger population-based cohort of New York anglers who previously participated in a study focusing on fish consumption and health) as they began trying to become pregnant (1996–1998, preconception) and after a positive pregnancy test (prenatal). The 52 women that gave birth represented the study cohort. PCB congeners were quantified and subsequently categorised by purported biological activity (total PCBs, antioestrogenic PCBs, oestrogenic PCBs and other PCBs). Mean total PCB concentrations were higher at baseline (preconception) than during the prenatal period (5.6 vs. 4.7 µg/l). Median preconception total PCB levels when grouped into tertiles were 4.6 (range 4.1–5.0), 5.3 (5.1–5.4) and 6.3 (6.2–7.0) µg/l. The relation between preconception PCB concentrations and birth weight varied with PCB grouping. For antioestrogenic PCBs, a 471 g reduction in birth weight was reported for women in the highest compared to the lowest tertile of exposure when adjusting for study covariates ($p = 0.048$), whereas no such decrement was found for oestrogenic PCBs. Nor was there a significant decrease for total PCBs. Further, when exploring a possible interaction between PCBs and infant sex, no significant effects were observed (274).

However, decreased male/female ratio following maternal exposure to PCBs from contaminated sport-caught fish was observed in a retrospective cohort study, whereas there was little evidence of an association with paternal exposure. Parental serum PCB concentration was examined in relation to the sex ratio of 173 children

of mothers and 208 children of fathers from the Great Lakes, US between 1970 and 1995. The adjusted OR for having a male child was reduced by 82 % (OR 0.2, 95 % CI 0.1–0.6) among mothers in the highest quintile of serum PCB concentration compared to the lowest quintile. No association was found between DDE concentration and sex ratio. The geometric mean of serum PCBs in mothers was 4.7 µg/l (range 3.0–12.1) in the highest quintile compared to 0.7 µg/l (0.5–0.9) in the lowest quintile. Serum measurements were made several years after the birth (416).

Decreased birth weight (and growth during early life) and nail malformations were commonly reported among children exposed *in utero* in the *Yusho* and *Yu-Cheng* incidents, but it should be kept in mind that there was exposure to relatively high concentrations of PCDFs and other structurally related chemicals in both poisoning episodes (19, 41, 91). No alterations of the sex ratio among children of exposed mothers were found following the poisonings (416).

In a review by Wigle *et al*, some epidemiological evidence was presented showing that maternal high-level exposure to PCBs/PCDFs and related compounds (i.e. the Asian rice oil poisoning incidents) can produce developmental tooth abnormalities, including hypomineralised enamel defects of permanent teeth. However, the evidence for maternal background PCB exposure was considered by the authors to be inadequate (420).

In a Slovenian study (cited in the review), 202 children living in a PCB-contaminated region and 202 matched controls were investigated. TEQ-intake from food was estimated to be approximately 40 pg TEQs/kg bw/day in exposed children. The percentage of PCB exposed children and of controls with defects of enamel in at least one permanent tooth was 71 % and 50 %, respectively ($p = 0.0019$). The enamel was abnormal in 22 % and 13 % of the permanent index teeth of exposed and control children, respectively ($p = 0.0001$). No significant correlations were found between PCB exposure and developmental effects in deciduous teeth (195).

A later study included 208 Slovakian children (8–9 years of age) living in an area where PCBs from a chemical plant had contaminated the surrounding district, and 224 children from a less exposed area. Mean TEQ levels of PCB in serum were 40 times higher than background levels in samples from the heavily polluted area. The children were categorised into three groups according to their serum PCB concentration (< 200, 200–600, > 600 ng/g lipid). A dose-response relationship between PCB exposure and developmental enamel defects of permanent teeth in children was observed. PCB exposure was significantly associated with developmental enamel defects of deciduous and permanent teeth in bivariate analysis, but in multivariate linear regression analysis PCB exposure was significantly related to enamel defects of permanent teeth only (194).

11.4.2.2 Neurodevelopment

Significant associations between PCB exposure and child neurodevelopment and cognition have been found in some studies but not in others. A number of neurobehavioural functions have been reported to be associated with pre-/neonatal exposure to polyhalogenated aromatic hydrocarbons, mainly PCBs, although discrepancies exist in terms of the spectrum of effects (neuromotor vs. cognitive), per-

sistence of effects and effective matrix (maternal vs. cord serum or breast milk) (424). Also, the laboratory procedures used for PCB exposure analysis vary across studies (cohorts). To facilitate a future comparison of studies of neurodevelopment, Longnecker *et al* (249) made an attempt to express the exposure levels from 10 such studies of PCBs in a uniform manner using a combination of data from original investigators, laboratory reanalyses, calculations based on published data, and expert opinion. The mainstay of the comparison was the median level of PCB 153 in maternal pregnancy serum (Table 17, page 119). If the concentration of PCB congeners responsible for the toxicity is proportional to that of PCB 153, the latter is likely to give a useful indication of the relative exposure level across studies. Still, there are differences between the cohorts, e.g. in the ratio of median concentrations for PCB 118/PCB 153, which was 0.18–0.87 (249). Also, it was reported in a recent review that the studies demonstrating the larger number of significant effects on cognitive functions were not the most highly exposed cohorts (41). Overall, EFSA came to the conclusion that there are indications that subtle developmental effects caused by non-dioxin-like PCBs, dioxin-like PCBs or PCDDs/PCDFs, alone or in combination, may occur at maternal body burdens only slightly higher than those expected from the average daily intake in European countries (98).

The associations between biological markers of prenatal PCB exposure and performance of cognitive tasks reported in studies from nine prospective longitudinal birth cohorts were summarised and classified by Boucher *et al* (41). It was suggested that prenatal PCB exposure affects only certain cognitive functions rather than all aspects of cognitive functioning in children. The most consistent effects observed across studies were impaired executive functioning. Negative effects on speed of information processing, verbal abilities and visual recognition memory were also reported in most studies. It was suggested that all these detrimental effects could be responsible for the IQ effects observed in some cohorts. A brief summary of the results from different cohorts are given in Table 18 (detailed information on type of tests and test results are given in Boucher *et al*). The authors considered it unlikely that coexposure with another contaminant was responsible for the observed effects, since the results were converging, although there were different sources of PCB exposure (fish, dairy products, meat). However, it was also stated that executive functions are sensitive to several disorders such as attention deficit and hyperactivity disorder, autism and obsessive-compulsive disorder, and exposure to other neurotoxicants e.g. lead (41). Some of the studies emerging from the cohorts are briefly described below.

Neurodevelopmental effects were investigated in a prospective longitudinal study of 242 infants born to mothers who had consumed contaminated fish from Lake Michigan and 71 infants born to mothers who were non-consumers (the Michigan cohort). The mean PCB levels in maternal serum were 6.1 µg/l among the fisheaters and 4.1 µg/l among the non-consumers. Dioxins and dioxin-like PCBs were not measured.

Consumption of contaminated fish and levels of PCBs in umbilical cord serum was positively correlated with lower birth weight, smaller head circumference and shorter gestational age. Also, fish consumption (but not cord serum PCB levels) was positively correlated with impaired autonomic function and increased number

Table 18. Neurobehavioural effects in children of prenatal PCB exposure (simplified scheme based on the review by Boucher *et al*, 2009 (41)).

Cohort (birth year)	Median [a] serum PCB 153 (ng/g lipid)	MDI	PDI	IQ total	Verbal functions	Visual-spatial functions	Verbal and/or visual memory	Attention	Executive functions	Auditory and/or visual functioning	Motor function
Japan, Hokkaido (2002–2004)	23	↔	↔	−	−	−	−	−	−	−	−
US, Oswego [b] (1991–1994)	40	−	−	↓	↓	↓	↓	↔	↓	−	−
US, North Carolina (1978–1982)	80	↔	↓	↔	−	−	↔	−	−	−	−
The Netherlands (1990–1992)	100	↔	↓	↓	↓	↔	↓	↓	↓	−	↓
Canada, Nunavik [c] (1995–1998)	100	−	−	−	−	−	−	−	−	↔	↔
US, Michigan (1980–1981)	120	↔	↔	↓	↓	↔	↓	↓	↓	−	↔
Germany (1993–1995)	140	↓	↓	↓	−	−	↔	−	−	−	−
US, CPP (1959–1965)	140	↔	↔	↔	−	−	−	−	−	↔	−
Denmark, Faroe Islands (1986–1987)	450 [d]	−	−	−	↔	↔	↔	↔	−	↓[e]	↔

[a] Estimated in maternal serum.
[b] State of New York.
[c] Cohort Northern Quebec.
[d] Estimated from maternal serum specimens collected in a later Faroese birth cohort.
[e] Hearing effect.
CPP: collaborative perinatal project, IQ: intelligence quotient, MDI: mental development index, PDI: psychomotor development index, US: United States.
−: not assessed, ↔: no significant effect, ↓: significant decreased performance on one or more of the measured parameters (tests).

of abnormally weak reflexes on neonatal behavioural assessment scale (NBAS) and significantly associated with decreased neuromuscular maturity measured on the Ballard Scale (19, 109, 188, 341). Cognitive functioning was assessed at 5 months, 7 months, 4 years and 11 years of age. Neither maternal fish consumption nor cord serum PCB levels were related to scores on the Bayley Scales of Infant Development at 5 months. In contrast, both exposure measures were associated with less preference for the novel stimulus on Fagan test of infant intelligence (a measure of visual recognition memory) at 7 months and cord serum PCB levels were the stronger predictor. Visual recognition memory was unrelated to neonatal variables such as birth size, gestational age and NBAS performance and to postnatal PCB exposure from nursing. At 4 years of age, cord serum PCB levels were associated with poorer performance on two tests involving short-term memory (McCarthy scales), whereas there was no indication of perceptive motor deficits or alterations of long-term memory. It was stated that the deficits were not attributable to exposure to polybrominated biphenyls, lead or seven other organochloride pesticides, since these variables were controlled for (19, 188, 192, 341). A re-analysis of the 4-year assessment indicated that the McCarthy memory scale and the general cognitive index declines were associated with prenatal PCB exposure only in the most highly exposed children (19).

At the follow-up at 11 years of age, the 30 most heavily exposed children (prenatal PCB exposure equivalent to at least 1 250 ng/g milk fat, 4.7 µg/l cord serum or 9.7 µg/l maternal serum) scored on average 6.2 points lower in full-scale intelligence quotient (IQ) in revised Wechsler Intelligence Scales for Children (WISC) test than those of the other four groups. However, some of the children in this group were markedly affected, whereas others appeared to be spared. Also, prenatal exposure to PCBs was associated with e.g. poorer word comprehension. The effects on word comprehension were largest in the two groups with the highest exposures (PCB $\geq$ 1 000 ng/g lipid in breast milk). Postnatal exposure to PCBs was not associated with a poorer performance on any of the tests. The effects on IQ and related effects were stronger in the non-breast-fed than in the breast-fed children (19, 188-190). Despite concerns about the design and analysis of the data from the Michigan Mother-Child studies, many of the findings in this cohort have been replicated in studies of other cohorts (19, 191).

In the Oswego study (State of New York, babies born 1991–1994), the pregnant women were divided into three groups based on estimated consumption of contaminated fish. Data indicated that new-borns in the high-exposure group demonstrated a greater number of abnormal reflexes and less mature autonomic responses (NBAS) compared to the other two groups (birth weight, head circumference and gestational age were unrelated to fish consumption) (19). In a subset of women (293 mothers: 141 who had and 152 who had not consumed contaminated fish), cord blood samples were collected for total PCBs and congener distribution pattern (68 PCB congeners) analysis. Dioxins, furans and coplanar congeners were not measured (341). The median total PCB concentration in cord serum was 0.52 µg/l (341, 375) and the median concentration of hepta- to nonachlorinated PCBs in cord blood was 0.05 µg/l (for values above the limit of detection) (373). The most highly exposed children showed significantly poorer performance on two clusters

of the NBAS. PCB exposed infants had more abnormal reflexes and tremors and were also over-reactive to stimulation failing to habituate to repeated auditory, tactile and visual stimulation. Only hepta- to nonachlorinated PCBs were correlated to NBAS performance, whereas PCBs of light (1–3 chlorines) or moderate (4–6 chlorines) chlorination were unrelated to NBAS performance, as were DDE, mirex, hexachlorobenzene, lead and mercury (316, 375).

In a subsequent study, linear trend analyses revealed a significant linear association between total PCBs in cord blood and declining Fagan test of infant intelligence performance at 6 and 12 months of age after control for all covariates. For hepta- to nonachlorinated PCBs (cord blood), a significant linear association was not observed at 6 months but was found at 12 months and the proportion of variance explained by these highly chlorinated PCBs was 2.3 %. A significant influence of prenatal methyl mercury, DDE or lead exposure on infant performance on this particular cognitive task seemed to be ruled out. No associations between total PCB levels in breast milk and Fagan test of infant intelligence performance at 6 or 12 months were observed, but the number of breast-feeders was small (85). At 38 and 54 months of age, 212 children participated in a study assessing cognitive development using McCarthy Scales of Children's Ability. PCB exposure was significantly related to poorer performance at 3 years of age, although not on the motor subscale. The tertiles of the distribution of subjects with detectable levels of hepta- to nonachlorinated PCBs in cord blood were > 0, > 0.02 and > 0.09 µg/l. After control for covariates, including methyl mercury and DDE, linear trend analyses revealed a significant, dose-related decline in general cognitive index performance at 38 months of age both for wet weight ($p = 0.012$) and lipid-adjusted ($p = 0.008$) values. Hepta- to nonachlorinated PCBs in cord blood were statistically significant predictors of small but measurable deficits in performance in the highest exposure-group. No significant associations for PCBs on McCarthy Scales were found at 54 months of age (316, 376).

Additional testing at 54 months of age, however, showed an association between prenatal PCB exposure, corpus callosum and impaired response inhibition (373). PCBs were associated with poorer performance in the Michigan Catch-the-Cat test, a variant of a continuous performance test. The increase in errors across the three testing blocks was directly proportional to the exposure, with statistically significant differences from the control group beginning at the intermediate exposure group (hepta- to nonachlorinated PCBs in cord blood > 0.02 µg/l). Magnetic resonance imaging scans at approximately 7.8 years of age in the 30 most exposed children and 30 of those least exposed matched on sex and handedness showed that there was a larger association between PCBs and impaired response inhibition when the splenium was smaller (316, 373). The increase in error rate was not mediated by global cognition, and was found in PCB exposed children with otherwise normal McCarthy scores (373, 374).

A follow-up assessment using the NES2 continuous performance test was conducted at 8 years of age. These findings were then followed up at 9 1/2 years of age by a series of extended continuous performance tests designed to dissociate response inhibition from sustained attention. After taking into account more than 50 measured covariables, including maternal IQ, maternal sustained attention and

maternal response inhibition, results revealed PCB-related associations with impulsive responding at both testing ages. Significant increases in commission errors were seen in the highest exposure group (hepta- to nonachlorinated PCBs in cord blood > 0.09 µg/l). These results were significant after extensive and rigorous control for multiple potential confounders (374).

The North Carolina cohort consisted originally of 880 pregnant women and assessed general population exposure. The median maternal serum PCB level at birth was 9.1 µg/l. PCB levels in milk averaged 1 800 ng/g lipid at birth and was used as indicator of prenatal exposure. However, other authors have stated that actual PCB concentrations were probably lower (19, 341) and as pointed out by the EU commission, dioxins and dioxin-like PCBs were not measured (109). The multiple regression analyses revealed no associations between birth weight or head circumference and PCB level. Neuropsychological outcome measures at birth included scores on the NBAS. Infants born to mothers with PCB concentration above 3 500 ng/g lipid in breast milk had less muscle tone, lower activity levels and were hyporeflexive. Infant cognitive and motor development was assessed by administering the Bayley Scales of Infant Development at 6, 12, 18 and 24 months of age. Higher transplacental exposure to PCBs was associated with lower psychomotor scores (psychomotor development index) at 6, 12 and 24 months of age. The children in the two groups with the highest PCB exposure (> 3 500 ng/g lipid in breast milk at birth) had adjusted scores on the psychomotor development index scales that were about 8 points lower (significant) than the scores of the children in the lowest exposure category. There was no relationship between prenatal PCB exposure and scores on the mental development index, and postnatal exposure through breastfeeding was unrelated to performance on either scale. Further, the deficits were no longer apparent at 3, 4 and 5 years of age when tested at McCarthy scales. It should be noted that 88 % of the women breast-fed their infants (19, 317, 341).

A large prospective study was carried out on 418 mother-infant pairs from two areas (Rotterdam, Groningen) in the Netherlands (some assessments were made only on children from one area). Prenatal PCB exposure was estimated by the sum of congeners 118, 138, 153 and 180 in maternal third trimester plasma and cord plasma (341). The mean concentrations of these PCBs in plasma and cord plasma were 2.2 and 0.4 µg/l, respectively. Also, PCB exposure was assessed in breast milk samples as the sum of the four PCBs or the sum of 20 non-dioxin-like PCBs. Furthermore, the dioxin-like PCBs 77, 105, 118, 126, 156 and 169 as well as PCDDs and PCDFs were estimated in breast milk and the mean total TEQ level (including PCDDs and PCDFs) was 67 pg/g lipid. PCB levels in maternal and cord plasma were not associated with either the reflex or postural cluster scores during the neonatal period (Prechtl's neurological exam), although breast milk PCBs and total TEQ at 2 weeks were associated with lower optimality score and hypotonia (Prechtl's neurological exam). The birth weight of children exposed to high cord plasma PCB levels (0.8 µg/l) were lower than that of children exposed to low levels (0.2 µg/l). Further, both cord and maternal plasma PCB levels were significantly associated with lower growth rates until 3 months of age in the formula-fed group (19, 188, 341, 429).

At 3, 7 and 18 months of age, Bayley Scales of Infant Development were used and both mental and psychomotor development indexes were included in the assessments. No relationship between neonatal thyroid hormone levels and mental or psychomotor development at any age was found. Prenatal exposure to PCBs (maternal blood) was significantly associated with a decrease in the psychomotor development index score at 3 months of age but not at 7 and 18 months of age. Postnatal TEQ exposure was associated with decreased psychomotor development index scores at 7 but not at 18 months. The mental development index scores were not significantly associated with either prenatal or postnatal PCB exposure. Neurological examination (motor functions) indicated that transplacental PCB exposure was associated with a small deficit in neurological condition at 18 months of age (PCB or dioxin exposure via breast milk was not). However, follow-up evaluations including both neurological and cognitive outcomes at the age of 42 months indicated that the neurological condition was not affected by pre- or postnatal PCB exposure, whereas the cognitive abilities (Kaufman assessment battery for children scales) appeared to be related to prenatal PCB exposure (especially to sum of PCBs in maternal blood). These negative effects were highly significant in the formula-fed subgroup, whereas none was significant in the breast-fed subgroup. In the group as a whole, a significant decline ($p < 0.05$) in scores on the scales was observed. Four point deficits in scales were reported, on average, for the highest exposure group (PCBs ≥ 3 µg/l maternal plasma) as compared to the lowest (< 1.5 µg/l). Cognitive performance was not related to either lactational exposure or current exposure to PCBs and dioxins (19, 188, 341, 429).

At 6.5 years of age, cognitive and motor abilities were assessed with the McCarthy Scales of Children's Abilities. Prenatal PCB levels were not related to general cognitive index, memory and motor skills after adjustment for covariables, although subtle negative effects of prenatal PCB and dioxin exposure were indicated when parental and home characteristics were less optimal. It was stated that it was uncertain whether the described effects of the sum of the four PCBs in plasma might also reflect effects of dioxins and other related organochlorine compounds. Postnatal exposure to PCBs and dioxins through lactation was not significantly related to cognitive or motor skills (429). Re-examination of the Rotterdam part of the Dutch cohort at 9 years age, however, revealed that higher prenatal PCB levels were associated with longer and more variable reaction times and lower scores on an executive function test. The latter also appeared negatively affected by lactational exposure to PCBs, although breastfeeding was associated with better scores. Likewise, the latencies on event-related potentials of the brain were longer at higher PCB exposure levels, but breastfeeding was associated with a decrease (98, 341).

In a similar study, the neurodevelopmental toxicity was investigated in 171 mother-infant pairs in Germany. The PCB concentrations (sum of PCBs 138, 153 and 180) were 0.55 µg/l (median 0.39) in cord plasma and 427 ng/g lipid (median 404) in breast milk. No PCDDs/PCDFs were measured. Neurodevelopment was assessed at 7, 18, 30 and 42 months of age. Outcomes measured at 7 months of age included determination of mental and psychomotor development indexes, and the Fagan test of infant intelligence. After adjusting for confounders, the only significant association was an inverse relationship between the sum of PCBs in milk

and mental development index scores. Significant inverse associations between maternal milk PCB concentrations 2 weeks after birth and scores on Bayley scales were observed at 30 months of age after adjustment for covariates, including scores on the HOME (home observation for measurement of the environment) scale. As PCB concentrations increased from the 5th to the 95th percentile, mental development index scores decreased by 9.9 points (roughly half that associated with the HOME score). Also, deficits on the Bayley psychomotor scales, which assess both fine and gross motor skills, were noted. Further, at 42 months of age, an inverse association between PCBs in breast milk at 2 weeks (index of prenatal exposure) and the mental processing composite index of the Kaufman ABC was observed. Also, a significant inverse association between postnatal PCB exposure and Kaufman ABC scores at 42 months of age was reported (11, 19, 188, 316, 341).

The mental and psychomotor development of 1 207 children, whose mothers were enrolled in the Collaborative Perinatal Project between 1959 and 1965 (from 12 centres across the US), was assessed at about 8 months of age using the Bayley Scales of Infant Development. The mean total PCB level (PCBs 28, 52, 74, 105, 118, 138, 153, 170, 180, 194 and 203) in maternal third trimester serum was 3.1 µg/l (range 1.24–16.3) and 95 % of the PCB concentrations were < 6.25 µg/l. No association between maternal serum PCB level and children's mental development index was detected. Neither did this study demonstrate any significant relation overall between prenatal PCB level and children's psychomotor development index, although the relation varied among study centres. None of the individual congeners were related to the mental or psychomotor development index when evaluated in separate models that combined all study sites (83). At 7 years of age, prenatal PCB exposure was evaluated in relation to cognitive tests (n = 894). The PCB-IQ association was examined in multivariate models and the results showed no association between *in utero* exposure to PCBs and lower IQ. The fully adjusted mean WISC full-scale IQ score was 93.6 among children in the lowest exposure category (< 1.25 µg PCB/l maternal 3rd trimester serum) and 97.6 among those in the highest exposure category (≥ 5 µg PCB/l). There was no indication that any congener was especially associated with IQ or that the association differed among congeners (140). At 8 years of age, 195 children with sensorineural hearing loss and 615 children selected at random, all in the Collaborative Perinatal Project US cohort, were compared. Nearly all the results were consistent with no association between *in utero* PCB exposure and performance on audiometric examination. Based on the average hearing threshold across the frequencies essential for speech recognition in the "worst ear", the maternal serum PCB level was unrelated to the adjusted odds of sensorineural hearing loss or to adjusted mean hearing threshold. The median exposures among the children with sensorineural hearing loss and those selected at random as reflected by the mother's third trimester serum total PCB concentration were 2.5 and 2.8 µg/l, respectively (247). Sensory measurements were also made in one Faroese cohort. No associations of PCB exposure with visual function were noted, but cord blood PCB concentrations were a significant predictor of increased auditory thresholds. However, only two frequencies were affected and the deficits were present only on the left side (341).

In a recent prospective study, the relation between prenatal exposure to PCBs and DDE and behaviours was investigated in children born to mothers residing near a PCB-contaminated harbour. The behaviour was assessed by using the Conners' Rating Scale for Teachers (CRS-T), where 4 of the 13 subscales are considered measures of behaviours associated with ADHD. Participants were born 1993–1998 in Massachusetts and umbilical cord blood samples were collected at birth. In total, 51 PCB congeners were measured (data available for 573/590 children). In the covariate-adjusted model, there was a consistent positive association between organochlorines and increased ADHD-like behaviours. For example, higher risk of atypical behaviour on the subscale Conners' ADHD index was seen for the highest versus lowest quartile of the sum of four PCBs (PCBs 118, 138, 153 and 180) (RR 1.76, 95 % CI 1.06–2.92). An increase in the sum of four PCBs in umbilical cord serum from the 5th to the 95th percentile resulted in an estimated 2.4-point increase in the index score. The other two PCB categories (sum of 51 PCBs and the computed TEQs for the sum of five dioxin-like PCBs) and DDE were associated with smaller effect estimates than the sum of four PCBs. The dose-response data indicated non-linearity and the authors stated that a threshold of effect was observed at the highest exposure quartile (327).

In the assessment of the cognitive development and behaviour of children born to *Yu-Cheng* parents, many findings have indicated that prenatal exposure to PCBs and their heat-degradation products, mainly PCDFs, produced long-lasting cognitive and behavioural damage as well as impairment in body control, large muscle coordination and skills of the hands. Slower mental and psychomotor development (Bailey Scales of Infant Development), cognitive impairment including lower IQ (Stanford-Binet test, revised WISC) and deficit in spatial ability (boys) have been reported. Further, prolonged latencies of auditory event-related potentials have been shown in some of the children. Also, some studies have indicated higher activity level, attention deficits and behavioural problems in *Yu-Cheng* children (144, 316, 341). Still, no correlation between the degree of deficit and the PCB levels of the mothers were seen (e.g. for lower IQ and behavioural disorders) (424).

11.4.2.3 Immune effects in offspring

ATSDR concluded that available data support a possible association between PCBs and immune effects in infants exposed *in utero* and/or by breast feeding. Although the studies are insufficient for determining which specific chemical(s) may be responsible for the observed alterations, the available data indicate a possible association between PCBs and immune effects that may be manifested as compromised ability to overcome infections (19).

EFSA reported that the number of infectious illnesses during the first 4 months of life was positively correlated with maternal serum PCB levels in children whose mothers had consumed contaminated fish. Likewise, associations were reported between risk of acute otitis media and increasing exposure to PCBs and other organochlorine compounds during the first year of life in infants of Inuit women (98).

In a Dutch study, effects of pre- or postnatal PCB/dioxin exposure were investigated in 105 breast-fed and 102 bottle-fed infants. The sum of PCBs 118, 138, 153 and 180 in maternal plasma and the total TEQ level (17 dioxins and 8

"dioxin-like" PCBs, including PCBs 170 and 180) in human milk (collected the second week after delivery) were used to estimate prenatal exposure. Postnatal exposure was calculated as a product of the total TEQs in human milk multiplied by the weeks of breast-feeding. The mean PCB plasma sum in the total group was 2.2 µg/l, and the mean total TEQ level was 66.6 pg/g lipid. There were no significant correlations between the number of periods with infections (otitis, rhinitis, bronchitis, tonsillitis) or plasma concentrations of antibodies to childhood vaccines during the first 18 months of life and pre- and postnatal PCB/dioxin exposure. In a subgroup of infants, white blood cell counts and immunological marker analyses in cord blood at 3 and 18 months of age were done. Prenatal PCB/dioxin exposure was associated with increases in T cell subpopulations in the blood, mainly at 18 months of age. The only significant association for the sum of four PCBs was for the number of $CD8^+$ T-cells (increase at 18 months). For total TEQs, significant increases were seen for the numbers of $TcR\gamma\delta^+$ T cells at birth, and $TcR\alpha\beta^+$ T-cells and $CD8^+$ T-cells at 18 months. Further, a higher prenatal exposure (total TEQs) was associated with lower monocyte and granulocyte counts at 3 months of age. Postnatal exposure was significantly associated with a decrease in B cell marker $CD\ 19/20^+$ and lower monocyte and granulocyte counts at 3 months of age. However, the results of the immunological marker analyses and of the white blood cell counts were all within the normal ranges of age-matched children (413).

Follow-up evaluations at 42 months of age showed that prenatal exposure to PCBs was associated with subtle decreases in antibody levels to mumps and rubella and increased T cell numbers. Antibody levels to mumps were inversely correlated with the sum of four PCBs (PCBs 118, 138, 153 and 180) in maternal plasma, and antibody levels to rubella inversely correlated with the sum of four PCBs in cord plasma. No significant correlations between antibody levels (mumps, rubella, measles) and the dioxin, planar and mono-*ortho* PCB TEQ levels (in human milk) separately or with the sum of four PCBs at 42 months of age were seen. White blood cell counts and immunological marker analyses of the lymphocytes at 42 months of age were available for a subgroup. The results were all within the normal ranges for age-matched children. Positive correlations (significant in the formula-fed subgroup) were found between prenatal PCB exposure (maternal and/or cord plasma) and the number of lymphocytes, T cells and subpopulations ($CD3^+CD8^+$, $CD4^+$ $CD45RO^+$, $TcR\alpha\beta^+$, $CD3^+$ $HLA\text{-}DR^+$) in blood. The median PCB level in maternal plasma was 2.1 (0.6–7.4) µg/l in the whole study group (n = 175) and 1.8 (0.6–4.8) µg/l in the subgroup (n = 85). Further, higher prevalences of recurrent middle-ear infections and of chicken pox, and a lower prevalence of allergic reactions were reported (parent questionnaire) to be associated with current PCB body burden in children (i.e. the sum of four PCBs in plasma at 42 months of age). However, no differences in the prevalences were seen between formula-fed and breast-fed children (median for sum of PCBs at 42 months was 0.2 vs. 0.8 µg/l). No significant associations were seen for these conditions in relation to prenatal PCB exposure (sum of four PCBs in maternal plasma). In breast milk, the mono-*ortho* and planar PCB TEQs were significantly associated with recurrent middle-ear infections (412). In a further follow-up study, a higher postnatal PCB

exposure through lactation was significantly associated with a higher prevalence of recurrent middle ear infections as assessed by parent questionnaire (414).

A decreased antibody response to vaccination was found among children in two Faroese birth cohorts exposed to high levels of PCBs early in life. The vaccinations started at 3 or 5 months of age and antibody analysis was done at 18 months (n = 119) and 7.5 years (n = 129), respectively. The antibody response to diphtheria toxoid decreased at age 18 months by 24 % for a doubling of the combined prenatal PCB exposure variables, whereas the tetanus toxoid antibody response was affected mainly at 7.5 years, decreasing by 16 % for each doubling of the prenatal exposure. However, the confidence intervals were wide. Geometric mean PCB concentrations in maternal serum (pregnancy) were about 1 200–1 300 ng/g lipid and were similar in serum of children at 18 months and 7.5 years of age (but did not correlate clearly). PCB burden in the early postnatal period was considered as the most important predictor of a decreased vaccination response. It could not be excluded that the measured PCBs were indicators of effects of other congeners or compounds. The effects of PCBs and DDE could not be separated (161).

In a Swedish study, it was suggested that background exposure to PCBs (and DDE) early in life modulate immune system development. Prenatal exposure was estimated from maternal serum samples (10 PCB congeners) donated in late pregnancy (1996–1999, 325 women). Infant health during the first 3 months was investigated by the use of a questionnaire and interviews. White blood cell counts (n = 86) and lymphocyte subset (n = 52) were analysed in a subgroup of infants at 3 months of age. The median prenatal exposure of the sum of PCBs 28, 52 and 101 was low (4 ng/g lipid, range 3–427). The infants with the highest prenatal exposure of these PCBs had significantly higher mean numbers of lymphocytes and monocytes than infants in the reference category. These infants also had an increased risk for respiratory infections (OR 3.4, 95 % CI 1.4–7.8) during the study period (3 months). On the contrary, prenatal exposure expressed as mono-*ortho*-PCB TEQs (PCBs 105, 118, 156 and 167) and di-*ortho*-PCBs (PCBs 138, 153, 180) were rather associated with decreased ORs for infection. The authors pin-pointed that the study was small and that the results should be interpreted with caution (132).

High prenatal PCB exposure has been associated with a decreased thymus size among neonates born in an area with high environmental load of both non-dioxin-like and dioxin-like PCBs in Eastern Slovakia. The thymus was measured on the third or fourth day after birth in 982 neonates. Maternal serum was obtained after delivery (2002–2004, n = 1 076). Fifteen PCB congeners were determined and 6 of these were included in the PCB sum (PCBs 118, 138, 153, 156, 170 and 180). The mean, median, 10^{th} and 90^{th} percentiles of the PCB sum were 620, 440, 190 and 1 170 ng/g serum lipid. The median level of PCBs 118, 138, 153 and 180 was 3.7 µg/l (288).

Children born to mothers accidentally exposed to PCBs (*Yu-Cheng*) had higher prevalences of bronchitis or pneumonia at 6 months of age, respiratory tract infections at 6 years of age and middle-ear infections at 6–14 years of age (19). However, it has been reported that the middle ear findings were associated with children's serum levels of PCDFs, but not of PCBs, suggesting stronger immunological effects of PCDFs than of PCBs (144).

11.4.2.4 Thyroid effects in offspring

Hypothyroid alterations in association with neonatal PCBs/polyhalogenated aromatic hydrocarbons at background environmental levels of exposure were reported in some early developmental studies in infants. However, in these studies, thyroid hormone levels were in the normal range (424). In the prospective Dutch study carried out on 418 mother-infant pairs (see Section 11.4.2.2), higher PCB/dioxin levels, expressed as TEQs, correlated significantly with lower plasma levels of maternal (during pregnancy and/or postdelivery) total T_3 and total T_4, and with higher plasma levels of TSH in infants in the 2nd week and 3rd month after birth. The mean total TEQ level (17 dioxins and 8 dioxin-like PCBs) in breast milk was 67 pg/g lipid (19, 188).

The association between transplacental exposure to various dioxin and PCB congeners and thyroid hormone status in 118 mother-newborn pairs from the general Taiwanese population was investigated in a more recent study. Data included dioxin/PCB levels (e.g. the 12 dioxin-like PCB congeners and PCBs 28, 52, 101, 138, 153 and 180) in the placenta and thyroid hormone status in the cord serum. Multivariate analysis showed independently and significantly decreased free $T_4 \times$ TSH levels with increasing non-*ortho* PCBs, most noteworthy in female infants, but the concentrations were within the normal range for cord blood (405).

The relationship between neonatal TSH levels and PCB congeners measured in mothers during pregnancy was investigated in a Mexican-American birth cohort (1999–2000, 285 women). The median PCB 153 concentration was very low (5.4 ng/g lipid). The geometric mean was 60 ng/g lipid for the sum of maternal PCBs based on 19 congeners and 0.9 pg/g lipid for TEQs. TSH levels were within the reference range for all children. Yet, a positive association between the sum of congeners suspected to be UDP-GT inducers (CYP2B inducers) and neonatal TSH levels was found. In individual congener analyses, PCBs 99, 138, 153, 180, 183, 187, 194 and 199 were positively associated with neonatal TSH levels after adjustment for covariates (PCBs 194 and 199 remained significant after adjustment for multiple hypothesis testing). No association was found with the sum of all PCBs or with dioxin-like PCBs (TEQs). However, PCBs 126 and 169 were not measured (63).

In a study of young Mohawks, the thyroid hormone profile was affected by exposure to a group of persistent PCBs (PCBs 74, 99, 105, 118, 138/163/164, 153, 180, 187). The PCB grouping was positively associated with TSH and inversely related to free T_4. Still, mean levels of total T_4, free T_4, T_3 and TSH were within the laboratory reference ranges. A group of non-persistent PCBs (PCBs 52, 70, 84, 87, 95, 101/90, 110, 149/123) was significantly and inversely related to free T_4 only. Additionally, the data on breast-feeding indicated that the effects for the group of persistent PCBs were primarily restricted to youth who had not been breastfed, but breastfed had higher levels of persistent PCBs and DDE (342, 343).

In a follow-up study (n = 115), the relationship between POP levels in blood and thyroid peroxidase antibodies, a biomarker of autoimmune disease, was examined (autoantibodies to thyroid peroxidase can impair thyroid function). Fifteen per cent of the samples had antibody levels above the normal laboratory reference range. After stratifying by breast-feeding status, participants who were breastfed showed

significant, positive relationships between antibody levels and all PCB groupings (two groupings according to Wolff *et al* (see Section 9.2), mono-, di-, tri/tetra-*ortho*-PCBs, UDP-GT inducing-based grouping) except the group of non-persistent PCBs (PCBs 52, 87, 95, 101/90, 110) and Wolff group 1 (PCBs 52, 70, 101/90, 187). Among the non-breast-fed group, no significant relationship was found with any of the toxicants (344).

In a recent study, TSH, total T_4, total T_3, free T_4 and free T_3 were measured in serum samples of pregnant women (n = 117–119) and in cord serum samples (n = 78–84), and dioxins, dioxin-like PCBs and six indicator PCBs were analysed in maternal blood during pregnancy and in maternal milk. The authors concluded that the study supports the view that exposure to PCDDs/PCDFs, dioxin-like PCBs and indicator PCBs, in total, at the current lower dose levels does not decrease serum thyroid hormone concentrations in pregnant women and new-borns (421).

No significant association between TSH in blood of new-borns and umbilical cord serum level of PCBs 118, 138, 153 and 180, and their sum, was reported in another recent study including 453 infants (251).

11.4.2.5 Other endocrine-related effects in offspring

In a study of mother-infant pairs in Germany (Duisburg cohort) PCDDs/PCDFs, dioxin-like PCBs and the sum of six indicator PCBs (PCBs 28, 52, 101, 138, 153, 180) were measured in maternal blood during pregnancy and in maternal milk. Testosterone and oestradiol concentrations were measured in cord serum (and maternal serum). The median concentration of indicator PCBs in maternal blood was 149 ng/g lipid. Some effects were seen on the hormone levels in babies, but the impact of PCDDs/PCDFs, and, to a lesser extent, that of structurally related PCBs, appeared to be more pronounced than that of indicator PCBs. Typically, testosterone reduction was more pronounced in cord serum of female babies and oestradiol reduction more pronounced in that of male babies. The authors stated that causal inferences can only be drawn with caution (55).

In a review by den Hond and Schoeters (91), epidemiological research on effects of endocrine disrupters on human puberty was summarised. Age at menarche or pubertal stages in girls was not related to PCBs in any of three referred studies with prenatal or prenatal and lactational exposure or in a fourth study with pubertal exposure. However, only total PCBs or a few single PCBs in serum were measured. All studies included different groups of the general population (e.g. the Michigan angler cohort, North Carolina cohort). In a later study by the same authors (90), a delay in timing of menarche in Flemish girls was reported. Exposure to oestrogenic PCBs was associated with a greater probability of having reached menarche in a study of young Mohawk girls (see Section 11.1.7).

In girls exposed prenatally (PCDFs/PCBs) during the *Yu-Cheng* incident, serum levels of oestradiol and follicle-stimulating hormone were increased at puberty. The girls also showed a shorter duration of menstrual bleeding and irregular menstruation as compared to controls (151).

The review by den Hond and Schoeters also summarised studies in boys. No effect on pubertal stages or testicular volume was shown in boys exposed to PCBs

prenatally or prenatally and during lactation (North Carolina cohort, Faroese birth cohort). However, in a study of villages in Belgium with pubertal PCB exposure of boys, there was an inverse association between serum PCBs and pubertal stages. Testicular volume was significantly lower in areas with higher PCB exposure but was not related to pubertal exposure to PCBs. It was speculated that this might be more closely associated with maternal exposure to endocrine disrupters during pregnancy (91). In a later study (90), higher serum levels of PCBs were associated with earlier sexual maturation in Flemish boys (see Section 11.1.7).

Risk of hypospadias and cryptorchidism in male offspring in relation to maternal pregnancy levels of PCBs was investigated in a study with nested case-control design. Third-trimester serum samples from the mothers of 230 sons with cryptorchidism and 201 sons with hypospadias and 593 sons with neither condition were analysed. The mothers were enrolled in the Collaborative Perinatal Project cohort between 1959 and 1965 (11 US cities, see Table 17, page 119). Serum levels of 11 congeners (PCBs 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) were measured and analysed separately and in different groups (i.e. Wolff groupings (see Section 9.2), low-/high-molecular weight groups, TEF group). The median for sum of PCBs in the three groups of mothers were 2.8 (cryptorchidism), 2.9 (hypospadias) and 2.7 (controls) µg/l. No notable associations with individual PCBs or with functional groupings of PCBs were found. For the sum of PCBs, the ORs (95 % CI) associated with hypospadias in the 2nd to 4th exposure categories (2–2.9, 3–3.9, ≥ 4 µg/l) were as follows: 1.6 (1.1–2.3), 1.4 (0.9–2.3) and 1.7 (1.1–2.7), with a p-value for trend of 0.08. The authors concluded that, given the large number of associations examined, these findings do not strongly support the hypothesis that PCBs are associated with cryptorchidism or hypospadias. Further according to the authors, no relationship between PCB levels in cord blood and cryptorchidism was found in a study of 196 Faroe Island boys born 1986–1987, and a study in Greenland indicated that PCBs might be inversely associated with risk of hypospadias (266).

In a prospective French case-control study on cryptorchidism, a somewhat higher (not significant) median level of sum of PCBs (PCBs 28, 52, 101, 118, 138, 153, 180) in maternal breast milk (colostrum) for cases than for controls (56 cases, 69 controls) was reported. A significant association between cryptorchidism and PCB level in milk was observed when the degree of exposure for cases and controls was divided into categories (unquantifiable values or values below or above the median). The OR in the highest category of PCB exposure was 2.7 (95 % CI 1.1–6.5, $p < 0.022$). However, when the analysis was restricted to the boys who remained cryptorchid at 3 months of age, the relationship with breast milk was no longer significant. Further, no significant associations were seen between PCBs in cord blood (67 cases, 84 controls) and cryptorchidism. The authors assessed that higher concentrations of selected xenobiotics in cryptorchid boys could be a marker of a higher global exposure and/or of a decreased capacity to metabolise and eliminate xenobiotics in general and that it is unlikely that a single compound is responsible for cryptorchidism (50).

In a recent case-control study, no significant increase in risk for hypospadias in offspring was reported for mothers whose serum PCB concentration was above the

median. The adjusted ORs (95 % CI) were 1.8 (0.5–6.4) for PCB 118, 1.2 (0.3–4.4) for PCB 138, 1.9 (0.5–7.1) for PCB 153, 3.9 (0.9–17) for PCB 180 and 1.9 (0.5–6.9) for the sum of PCBs. Still, the mean concentration of PCB 118 in maternal serum (0.07 vs. 0.04 ng/g) differed significantly ($p = 0.023$) between the 37 cases and 21 controls (131).

Hardell *et al* reported in a case-control study that mothers of patients with testicular cancer had an increased PCB body burden compared to mothers of controls ($p = 0.0006$). The sum of PCBs, and 19 of 37 analysed PCB congeners in blood were significantly increased among the case mothers. Case mothers also showed highly significant increased concentrations of *cis*-nonachlordane and hexachlorobenzene. A priori decided grouping of PCBs (according to Wolff *et al* (see Section 9.2); TEQs according to Ahlborg *et al* (1)) yielded for potentially oestrogenic and weak phenobarbital inducers an OR of 2.4 (95 % CI 0.95–6.0), for phenobarbital, *CYP1A* and *CYP2B* inducers an OR of 2.6 (95 % CI 1.03–6.5) and for dioxin-like PCBs an OR of 3.3 (95 % CI 1.3–8.4). Adjustment was made for body mass index and age in the mothers. It cannot be excluded that the real etiological agent was something unknown. As the mothers' blood samples were obtained many years after their sons were born it is unclear to what extent the mothers' PCB levels reflected the levels during pregnancy. No differences were found between the concentrations of PCBs in cases and controls (155, 156).

Decreased semen quality was seen in a small study on men exposed prenatally to high levels of PCBs and PCDFs after maternal ingestion of contaminated rice oil (*Yu-Cheng*). Increased per cent abnormal sperm morphology and decreased percentage of motile and rapidly motile sperm was seen in the 12 exposed men compared to 23 unexposed controls. Reduced ability of sperm from exposed men to penetrate the hamster oocyte was shown. No statistical adjustment for confounders was done in these studies, although age and percentage of smokers were similar in exposed and unexposed groups (158). Also, decreased serum testosterone levels together with increased oestradiol and follicle-stimulating hormone levels at puberty have been reported in boys previously exposed prenatally to PCDFs/PCBs during the *Yu-Cheng* accident (151). Further, boys born in the early years after the *Yu-Cheng* accident had reduced penile length compared to controls, but it should be kept in mind that there was exposure to relatively high concentrations of PCDFs and other structurally related chemicals (19, 91).

12. Dose-effect and dose-response relationships

12.1 Animal data

Animal studies with inhalation exposure to PCB mixtures are scarce and are considered inadequate for identifying dose-effect/dose-response relationships. At oral administration, many different effects have been shown in studies of PCB mixtures or PCB congeners. Species differ in sensitivity, e.g. monkeys seem to be more sensitive than rodents.

Many of the effects reported in animals exposed to PCB mixtures are hallmarks of dioxin-like compounds. The dioxin-like PCBs are considered to be the most

toxic PCB congeners, although the potency differs considerably within the group. The most toxic congener, PCB 126, occurs at very low levels in PCB mixtures. The non-dioxin-like PCBs may have effects on the same organ systems as the dioxin-like, albeit generally at higher doses. For neurobehavioural effects in offspring, some data indicate that the non-dioxin-like PCBs might be of importance.

The effects occurring at the lowest dose levels of PCB mixtures (5–7.5 µg/kg bw/day) are effects on skin/nails and eyelids, immune system, reproduction and development (Table 19).

Dermal and ocular effects, including nail changes and inflammation and/or enlargement of the tarsal glands, as well as decreases in IgM and IgG antibody responses to sheep red blood cells and increased plasma triglyceride levels were reported in adult female rhesus monkeys at long-term daily ingestion of 5 µg/kg bw Aroclor 1254 (the lowest dose studied) (15, 29, 386, 387). In addition, resorptions, foetal and post-partum death occurred for 6/10 impregnated monkeys dosed similarly with Aroclor 1254 before and during gestation (and during part of the lactation). Nail bed prominence was seen at birth and other slight toxic effects i.e. ocular, dermal and immunological effects developed later in the infants (13).

Hyperpigmentation during nursing and increased locomotor activity at 12 months of age were reported in infants of female rhesus monkeys given Aroclor 1248, corresponding to approximately 6.3 and 13 µg/kg bw/day, before and during gestation and lactation (6, 43, 336), but without a clear dose-effect relationship.

Mild effects on the immune system (e.g. reduction over time of IgM and IgG antibodies to sheep red blood cells) were shown in monkeys dosed from birth to 20 weeks of age with 7.5 µg/kg bw/day of a PCB mixture with a composition similar to that found in human breast milk. The weakly dioxin-like PCBs 105, 118, 156, 157 and 189 contributed to almost one fourth of the mixture. Changes were observed in neurobehavioural tests performed at 2.5–5 years of age suggesting a learning deficit and difficulties in adaptively changing response pattern, e.g. inability to inhibit inappropriate responding (14, 308).

Some hyperpigmentation was observed in neonates of rhesus monkeys given approximately 7.5 µg/kg bw/day Aroclor 1016 in the diet, before and during gestation and lactation. At daily doses of 30 µg/kg bw, decreased birth weight was also observed as well as effects on learning in infants tested at 14 months and at 4 years of age. However, a significant decrease in performance at 4 years of age was observed only when compared to the low-dose group and not compared to controls (27, 235, 335, 336).

Thyroid effects manifested as changes in serum T_3 and/or T_4 levels have been observed in rats. Levels were increased following a 30-day exposure of 33 µg/kg bw/day of Aroclor 1242, whereas long-time exposure to 90 and 100 µg/kg bw/day of Aroclor 1254 resulted in decreased levels. In rat offspring, depressions in both serum total T_4 and T_3 concentrations were seen at a similar dose level. Dams were dosed with about 100 µg/kg bw/day Aroclor 1254 during gestation and lactation, and pups also via diet through postnatal day 30 (19, 54, 59, 141, 303).

Decreased spermatogenesis was seen in 1 of 4 monkeys fed a diet providing approximately 100 µg/kg bw/day of Aroclor 1248 for one year (6, 19).

PCB mixtures are known tumour promotors and considered as animal carcinogens. Several studies have shown that PCB mixtures induce tumours in rodents, especially in the liver, but these data do not indicate that PCBs are multiorgan carcinogens. Cancer has occurred only at PCB dose levels far in excess of those inducing other effects. Data indicate that total TEQ-doses (associated with dioxin-like constituents within the technical mixtures) rather than total PCB doses, are mainly, if not exclusively, responsible for the development of liver neoplasms in female rats (19, 49, 98, 185, 186, 264). Overall, the results of *in vitro* and *in vivo* genotoxicity studies indicate that technical PCB mixtures are not directly mutagenic, but indirect genotoxic mechanisms of PCBs involving oxidative DNA damage have been described (19, 49, 98, 196, 280). However, there are studies suggesting that some single PCB congeners/metabolites are mutagenic (98, 122, 234, 432). The most potent dioxin-like PCB congener, PCB 126, is considered a complete carcinogen in experimental animals (24, 280).

12.2 Human data

Several epidemiological studies investigating health effects of occupational PCB exposure are old or studies on formerly exposed cohorts. In these studies, many workers were exposed to high PCB levels as compared to present occupational PCB levels in the Nordic countries. Also exposure scenarios and, to some extent, analytical methods and endpoints studied differ from today's situation. More emphasis is therefore put on studies on more recent, low-level exposures.

Studies of workers involved in removal of PCB-containing sealants or employed at waste disposal plants indicate that exposure levels nowadays, assessed as blood PCB concentrations, are within the range of that of the general population (Tables 8–12 in Chapter 6, and Table 20). Still, compared to pre-exposure values or control groups, total PCB levels in plasma/serum seem to be slightly elevated in occupationally exposed. This may, at least in part be due to historical occupational exposure. Studies on health effects in workers occupationally exposed to low concentrations of PCBs are few (Table 20), whereas there is an extensive body of literature concerning health effects in groups of the general population.

For the general population as well as the occupationally exposed, food ingestion is a major route of PCB exposure. This exposure is particularly to the more persistent higher chlorinated PCBs. In subgroups, there is also exposure to airborne, mainly low-chlorinated PCBs, originating e.g. from PCB-contaminated buildings. In Sweden, the calculated median daily intake via food of non-dioxin-like PCBs (sum of 23 congeners) in adults during the late 1990s was 5.5–12 ng/kg bw. However, in Baltic Sea fishermen, the corresponding intake from fish could reach 80 ng/kg bw or even more. In many European countries, the daily PCB intake by breastfed infants is significantly higher (per kg bw) than that by adults (98).

A comparison between studies is difficult, e.g. because of differences in the number of PCB congeners measured and the variable presence of contaminants in technical PCB mixtures (dioxin-like substances, e.g. PCDFs). It is also difficult to distinguish the impact of the PCBs in relation to other environmental pollutants, especially since the concentrations of several compounds correlate with each other.

Nonetheless, some concluding remarks on possible associations between PCB exposure and health effects, mainly at low or rather low exposure, are given below. In some studies, the plasma/serum level of one of the dominating PCBs, the hexachlorinated PCB 153, was used as a marker of the total PCB exposure.

Thyroid effects

In the general population, the relationships between PCB exposure and thyroid hormone status have been investigated in a number of studies. A lack of consistency in reported correlations between studies has been found (150). Part of the inconsistency of the epidemiological study results might be explained by exposure to other endocrine disrupting chemicals. Some studies indicate an inverse association between PCB serum/plasma concentrations and mainly T_3 and/or T_4 levels (329). Mean/median levels of PCBs in serum/plasma in these studies were 220–850 ng/g lipid, but the number of measured PCB congeners differed (Table 15, page 86).

In a recent occupational study, no evidence for effects on thyroid function was found in Swedish male workers with at least 6 months experience of removing old elastic PCB-containing sealants in the two previous years (2000–2001). The mean plasma PCB level as sum of 19 congeners was 2.3 µg/l (580 ng/g lipid) in exposed workers as compared to 0.9 µg/l (260 ng/g lipid) in controls. The mean plasma concentration of PCB 153 in exposed workers was 0.51 µg/l (130 ng/g lipid) (354).

As the data on thyroid effects are inconsistent, no definite conclusions can be drawn.

Diabetes

Studies on the general population suggest that persistent organochlorine compounds including PCBs may contribute to especially type 2 diabetes and that a high dioxin burden might be associated with an increased risk of type 2 diabetes or modified glucose metabolism (62, 72, 97, 110, 111, 222, 228-230, 232, 292, 311, 314, 323, 391-395, 406, 410). However, data are insufficient to allow any firm conclusions. The possibility of a reverse causality or that both PCB levels and diabetes are independently related to fat turnover cannot be ruled out.

In occupational studies (with high exposure levels), one study reported on elevated blood glucose levels among capacitor workers (226). Apart from that there is little support for a relationship between PCBs and diabetes, but other studies were crude in that only mortality was addressed (209, 246, 250, 300, 301).

Immunological effects

An association between PCBs and immune effects in adults of the general population has been suggested. Interpretation of the data is, however, complicated since responses were generally subtle and exposures included a number of other potentially immunotoxic persistent substances. Still, there are some data suggesting slight immune effects in infants exposed *in utero* and/or via breast feeding (see Developmental effects below) (19).

Information on immunological endpoints in occupationally PCB exposed is scarce. Weak dose-response relationships between plasma levels of PCBs 101,

138, 153 and 180 and some immune parameters were seen in patients who had been occupationally exposed to PCBs. Most of the patients had been exposed to PCBs for more than 20 years, but also to other chemicals suspected to induce immunological impairments. Blood levels of the various compounds were strongly correlated with one another. The patients had various symptoms including frequent common cold diseases and bronchitis, but it is unclear if these were related to PCB exposure. Mean plasma levels of PCBs 138, 153 and 180 were 0.7, 1.0 and 0.6 µg/l, respectively (82).

In a recent Swedish occupational study, no evidence of effects on the immune system was found in male workers removing old elastic PCB-containing sealants (study described above under thyroid effects). The mean plasma concentrations were 2.3 µg/l for the sum of 19 congeners and 0.46, 0.51 and 0.35 µg/l for PCBs 138, 153 and 180, respectively (354).

Hepatic effects

Although a positive correlation between serum PCB and γ-glutamyl transferase levels was reported in a study of people exposed to PCBs and other chlorine compounds via contaminated fish (19, 214), there is no clear indication that environmental low-level exposure to PCBs has caused adverse liver effects in humans.

In an old study of transformer repairmen with a rather low exposure to PCBs, subtle metabolic effects were indicated. Serum γ-glutamyl transferase levels were not different from that of controls but were significantly positively correlated with serum PCB levels, possibly indicating enzyme induction. An inverse correlation between urinary 17-hydroxycorticosteroid and adipose tissue PCB concentration was also reported. The PCB patterns resembled Aroclor 1260. Breathing zone sample concentrations of PCBs were ≤ 60 µg/m^3 and 8-hour TWAs of PCBs were 0.01–24 µg/m^3, but there was also PCB contamination of the hands (99-101). The measured total PCB serum median values as reported in a later study were approximately 43 µg/l for currently exposed workers, 30 µg/l for formerly exposed workers and 13 µg/l for controls (114).

Significant positive associations between plasma levels of PCBs 138 and 153 and γ-glutamyl transferase were reported in patients who had been occupationally exposed to PCBs. However, confounding factors such as alcohol consumption were not controlled for and plasma levels of PCBs were strongly correlated with those of other chlorinated compounds. Mean plasma levels of PCBs 138, 153 and 180 were 0.7, 1.0 and 0.6 µg/l, respectively (82) (study described above under immunological effects).

Cardiovascular effects

Some studies of the general population suggest an association between PCBs and hypertension. The authors emphasise that their results must be interpreted with caution because of the cross-sectional study design (112, 113, 136, 148, 393). The inherent problem associated with such study design is that the sequence in time of disorder and exposure is unknown, which precludes causal interpretations.

The possible relationship between PCB exposure and ischaemic heart disease has been investigated in a number of occupational cohort studies, but the results are inconsistent and dose-estimates are crude (146, 208, 250, 258, 300, 301, 321).

Cancer

The evidence from epidemiological studies for carcinogenicity of PCBs is insufficient and do not allow definite conclusions.

In the general population, epidemiological evidence is conflicting concerning increased cancer risks associated with PCBs. Nevertheless, several studies suggest a relationship between increased risk of NHL and increased PCB levels in serum/plasma, although the causality has not been clarified (34, 71, 87, 102, 153, 218, 319, 369).

Studies of highly exposed occupational cohorts have not consistently shown elevations of the same type of cancer and are thus of limited use in defining risk. Still, a few studies suggest a correlation between PCBs and increased risks of prostate cancer and possibly cancer of the liver and biliary tract, and malignant melanoma (19, 61, 146, 300, 301, 321), but the results must be corroborated in other studies.

The most potent dioxin-like PCB congener, PCB 126, was recently classified by IARC as a human carcinogen in Group 1 on the basis of animal cancer data in combination with mechanistic information (24).

Effects on male fertility

Some data suggest that PCBs may interfere with male reproductive function, but alternative explanations are possible. In some studies of the general population, an inverse association between serum PCB levels and sperm motility was shown, whereas there is generally no support for effects on sperm counts. Significantly decreased progressive sperm motility was observed across populations at serum PCB 153 concentrations above 200 ng/g lipid with a slight (non-significant) decrease already at 50–200 ng/g lipid (Table 16, page 112). Yet, no major impact of PCBs on fertility has been shown (38, 81, 158, 159, 269, 309, 313).

In the occupational studies, no clear indications of PCB-related reproductive effects in men have been reported, but these endpoints have not been extensively studied (100, 101, 114).

Developmental effects

Epidemiological data on prenatal growth and birth weight in the general population are conflicting (19, 98). However, some studies indicate an association between PCB levels in maternal or cord serum/plasma and a reduction in birth weight, at least at dose levels somewhat higher than those commonly occurring in the general population (170, 274, 328). Further, data on the general population indicate that subtle developmental effects involving neurobehavioural functions are associated with pre-/neonatal exposure to PCBs. Yet, discrepancies between studies exist, e.g. in terms of the spectrum of effects (neuromotor vs. cognitive) and persistence of effects. There is also a lack of dose-response relationships regarding cognitive functions using PCB 153 as a marker, but the levels of PCB congeners responsible

for the toxicity might not have been proportional to those of PCB 153. Other contaminants (including other dioxin-like compounds) may also have contributed to the effects. Assessed median PCB 153 levels in maternal serum were 40–140 ng/g lipid in the most affected cohorts (Table 18, page 123). Such concentrations are at the same level as, or slightly higher than, those commonly reported in the general population in recent years (41, 424).

There are also some data suggesting a sensitivity of the immune system to PCBs in infants exposed *in utero* and/or via breast feeding. Increases in lymphocytes (T-cells and subpopulations) in blood, decreased antibody response to vaccination and higher occurrence of infections have been reported. However, the specific chemical(s) responsible for the observed alterations cannot be identified (19, 161, 412-414).

13. Previous evaluations by national and international bodies

According to US EPA (1997), there is sufficient evidence for cancer from PCBs from animal studies. The human evidence were considered inadequate but suggestive of carcinogenicity (399).

The PCBs were evaluated by IARC in 1978 and 1987 (185, 186) and the evidence of carcinogenicity in laboratory animals was considered sufficient. IARC concluded that the available human studies suggested an association between cancer and exposure to PCBs and that the increased risk of hepatobiliary cancer emerged consistently in different studies. The evidence was, however, considered to be limited. Taking the combined evidence from human and experimental animal studies, the IARC group concluded that PCBs are probably carcinogenic to humans (Group 2A). PCBs were classified without distinction between dioxin-like and non-dioxin-like congeners (186). Recently, the dioxin-like PCB 126 was classified by IARC as a human carcinogen (Group 1) on the basis of mechanistic information and animal data. PCB 126 is a complete carcinogen in experimental animals (24).

WHO/IPCS (2003) stated that adverse health effects, including immunological, developmental and reproductive effects and effects on liver and body weight, were observed in experimental animals exposed to PCBs. Several studies consistently reported an increase in liver cancer incidence among rodents exposed to different PCBs. Further, IPCS concluded that human studies have identified associations between exposure to PCB mixtures and adverse immunological, reproductive and dermatological effects and cancer (mainly cancers of the digestive system, especially liver cancer, and malignant melanoma), but that limitations of the studies made it impossible to use them as a basis for quantitative risk estimations. It was mentioned that effects on sperm motility, foetal growth rate, development (e.g. neuromuscular immaturity) and neurological functions of the offspring (e.g. lower IQ scores and attention deficits) have been observed in studies on humans exposed to PCBs (188).

Table 19. LOAELs in animal studies of PCB mixtures at oral administration including dose levels up to 100 µg/kg bw/day.

PCB mixture	Species (strain), no. of animals	Daily dose (µg/kg bw)	Exposure duration	Effect	Reference
Aroclor 1254	Monkey (Rhesus), 16 females	5 [a]	37 mo	*Dermal and ocular effects:* Finger and toenail changes and inflamed and/or prominent tarsal glands (all effects also seen at 20, 40 and 80 µg/kg bw in a dose-related manner). *Hepatic effects:* Increased plasma triglycerides (also seen at 20 and 80 µg/kg bw).	(15, 29, 386, 387)
			23 and 55 mo	*Immunological effects:* Reduced IgM and IgG antibody response to SRBCs (also seen at 20, 40 and 80 µg/kg bw in a dose-related manner).	
Aroclor 1254	Monkey (Rhesus), 16 females (same as above)	5 [a]	37 mo pre-mating to 7 weeks post-parturition	*Reproductive and developmental effects:* Resorptions, foetal or post-partum death in 6/10 impregnated monkeys (effects seen also at 20, 40 and 80 µg/kg bw). Nail bed prominence at birth, inflammation or enlargement of tarsal glands, nail lesions, gum recession and reduced IgM antibody levels to SRBCs in infant offspring (effects also seen at 40 µg/kg bw, no surviving pups 2 weeks post-partum in the 20 and 80-µg/kg dose groups).	(13)
Aroclor 1248	Monkey (Rhesus), 8 females	6.3 [a, b]	Pre-mating to 4 mo post-parturition	*Developmental effects:* Hyperactivity in offspring (also seen at 13 µg/kg bw/day, but no clear dose-effect relationship). Hyperpigmentation developed during nursing in offspring (also seen at 13 µg/kg bw).	(6, 43)
Aroclor 1016	Monkey (Rhesus), 8 females	7.5 [a]	22 mo (7 mo pre-mating to 4 mo post-parturition)	*Reproductive and developmental effects:* Some hyperpigmentation at birth (also seen at 30 µg/kg bw).	(27, 235, 336)
15 PCBs resembling the composition in human milk	Monkey (Rhesus and Cynomolgus), 3/sex and 8–10 males, respectively	7.5 [a]	5 mo (1–140 days of age)	*Developmental effects:* Minimal reduction in IgM and IgG antibodies to SRBCs, reduced level of the cell surface marker HLA-DR and transient decrease in B lymphocytes. Deficits on delayed spatial alternation, fixed interval and differential reinforcement of low rate performance. (Only dose tested).	(14, 308)

Table 19. LOAELs in animal studies of PCB mixtures at oral administration including dose levels up to 100 µg/kg bw/day.

PCB mixture	Species (strain), no. of animals	Daily dose (µg/kg bw)	Exposure duration	Effect	Reference
Aroclor 1254	Monkey (Rhesus), 16 females	20	37 mo	*Haematological effects:* Decreased mean platelet volume (also seen at 80 µg/kg bw).	(12)
Aroclor 1254	Monkey (Rhesus), 15 females	20	37 mo pre-mating to 7 weeks post-parturition	*Reproductive and developmental effects:* Reduced conception rate (also seen at 40 and 80 µg/kg bw).	(13)
Aroclor 1016	Monkey (Rhesus), 8 females	30	22 mo (7 mo pre-mating to 4 mo post-parturition)	*Reproductive and developmental effects:* In offspring, reduced birth weight, decreased performance in spatial discrimination reversal learning and (compared to low-dose group) in delayed spatial alternation test. Improved performance on a shape discrimination-reversal problem.	(27, 235, 335, 336)
Aroclors 1242, 1248, 1254, 1260	Rat (Osborne Mendel), 6 males/mixture	30 [a]	4 weeks	*Hepatic effects:* Microsomal enzyme induction.	(245)
Aroclor 1242	Rat (Sprague Dawley), 8 males	33 [a]	30 days	*Immunological effect:* Thymic atrophy. *Neurological effects:* Slowed exploratory behaviour in open field test. *Endocrine effects:* Increased serum total T_3 and T_4 levels. (Only dose tested).	(59)
Aroclor 1254	Monkey (Rhesus), 16 females	40	37 mo	*Hepatic effects:* Decreased serum cholesterol (also seen at 80 µg/kg bw).	(12, 29)
Aroclor 1016	Mouse (CD-1), females	50 [a]	Gestation days 16–18	*Reproductive and developmental effects:* Increased anogenital distance in male (but not female) offspring. Decreased epididymal weight, increased prostate weight and increased androgen-receptor binding activity in prostate in offspring. (Only dose tested).	(145)
Aroclor 1254	Rat (Sherman), 10 males, 20 females	60 [a]	2 and 6 mo pre-mating, during mating, gestation and lactation	*Reproductive and developmental effects:* Increased relative liver weights in male pups in F_1 generation.	(244)

Table 19. LOAELs in animal studies of PCB mixtures at oral administration including dose levels up to 100 µg/kg bw/day.

PCB mixture	Species (strain), no. of animals	Daily dose (µg/kg bw)	Exposure duration	Effect	Reference
Aroclor 1254	Monkey (Rhesus), 16 females	80	37 mo, 72 mo	*Haematological effects:* Decreases in red blood cell count, haemoglobin concentration and haematocrit. *Hepatic effects:* Increased relative liver weights attributed to hyperplasia. Decreased serum levels of total bilirubin.	(12, 16)
Aroclor 1254	Rat (Sprague Dawley), 10 females	90 [a]	5 mo	*Endocrine effects*: Decreased serum total T_3 and T_4 levels.	(54)
Aroclor 1254	Rat (Sprague Dawley), 16 females	100 [a]	Gestation day 1 to 30 days post-parturition	*Reproductive and developmental effects:* Decreased serum total T_4 (not significant) and T_3 levels in pups at 30 days, increased choline acetyl-transferase activity in hippocampus and basal forebrain in pups at 15 days and decreased activity at 30 days.	(19, 303)
Aroclor 1254	Rat (Fischer 344), 30 males	100 [a]	15 weeks	*Bone effects:* Increased femur density. *Endocrine effects:* Decreased serum T_4 levels.	(9, 141)
Aroclor 1248	Monkey (Rhesus), 9 females	100 [a]	8 mo	*Dermal and ocular effects:* Acne, alopecia, erythema and swelling of the eyelids. *Hepatic effects:* Lipid accumulation, focal necrosis, increased serum GPT activity and decreased albumin/globulin ratio. *Systemic:* Body weight loss, 1 death.	(19, 26)
Aroclor 1248	Monkey (Rhesus), 8 females (same as above)	100 [a]	16–21 mo (pre-mating to 3 mo post-parturition)	*Reproductive and developmental effects:* In dams, increased menstrual duration and bleeding, and signs of PCB intoxication. Resorptions/abortions in 3/8. In offspring, decreased birth weight, a small stature and decreased body weight gain, hyperpigmentation at birth, and signs of PCB intoxication (acne, loss of eye lashes) within 2 months. Later, death of 2 infants, changes in thymus, spleen, bone marrow and liver. Impaired learning and hyperactivity.	(5, 6, 19, 26, 42, 43)
Aroclor 1248	Monkey (Rhesus), 4 males	100 [a]	18 mo	*Reproductive effects:* Decreased spermatogenesis in 1 of 4 animals.	(6, 19)

[a] Lowest dose tested.
[b] Administration 3 times/week, but recalculated to an average dose 7 times/week.
GPT: glutamic pyruvic transaminase, Ig: immunoglobulin, LOAEL: lowest observed adverse effect level, SRBC: sheep red blood cell, T_3: triiodothyronine, T_4: thyroxine.

Table 20. Dose-response relationships in some occupational studies with low/rather low exposure to PCBs.

Population	PCB content	Serum/plasma PCB levels (µg/l)		Results	Reference
		Exposed	Controls		
55 transformer repairmen, 56 controls	PCB patterns resembled Aroclor 1260 in all groups (27 PCBs quantified)	Serum [a] Median (mean) (range) Current exposure (n = 35) 42.6 (53.7) (4.3–253) Past exposure (n = 17) 29.9 (38.6) (1.5–143)	Median (mean) (range) 12.8 (20.0) (0.5–181)	*Hepatic effects:* Positive correlation between serum PCB and serum GGT levels; GGT not significantly different from controls. Inverse correlation between adipose tissue PCBs and 17-hydroxycortico-steroid excretion in urine. *Thyroid effects:* Slightly lower mean value for T_4 in serum, but no correlation between serum PCB levels and effect after adjustment for age. Neither was there a correlation with adipose tissue PCB levels. Few significant correlations between PCBs and the studied endpoints (serum liver function tests, thyroid function tests, haemoglobin and white blood cell counts, sperm count etc.).	(99-101, 114)
141 teachers, construction workers, telecommunication technicians etc. (patients)	PCB 28 PCB 52 PCB 101 PCB 138 PCB 153 PCB 180	Plasma, mean < 0.01 < 0.01 0.031 0.066 (95 % quantile) 0.71 1.44 (95 % quantile) 1.03 2.22 (95 % quantile) 0.6 1.07 (95 % quantile)	< 0.01 [b] < 0.01 [b] < 0.1 [b] < 0.5 [b] < 0.6 [b] < 0.3 [b]	*Immunological effects:* Weak dose-effect relationships between blood PCB levels and cellular and humoral immune parameters (*in vitro* lymphocyte stimulation, numbers of lymphocyte subpopulations, immunoglobulin autoantibodies). Undetectable IL-4 blood levels more frequent in patients with PCB 138 above the mean (> 0.7 µg/l) than below the mean. Low DR+ cell counts in blood more often in patients with PCB 101 above the mean (> 0.03 µg/l) than below the mean. *Hepatic effects:* Significant positive associations between PCB 138 and 153 plasma levels and GGT plasma levels (alcohol consumption was not controlled for). Different symptoms (e.g. frequent common cold diseases, bronchitis, irritation of mucous membranes of the throat and nose), but unclear if any of them were related to the PCB exposure. Also exposure to other chemicals suspected to induce immunological impairments. Blood levels of PCBs were strongly correlated with those of other chlorinated compounds.	(82)

Table 20. Dose-response relationships in some occupational studies with low/rather low exposure to PCBs.

Population	PCB congener no.	Plasma PCB level, µg/l		Plasma PCB level, ng/g/lipid		Endpoints studied and results	Reference
		Exposed [c] GM (range)	Controls GM	Exposed GM (range)	Controls GM		
36 workers removing old PCB-containing sealants, 33 controls	PCB 28	0.052 (0.0029–0.39)	0.011	13 (0.7–110)	3.2	*Thyroid effects:* No evidence of effects on thyroid function, as measured by serum levels of total T_3, free T_4 and TSH. No significant correlation with thyroid function parameters for individual PCBs (PCBs 28, 52, 101, 118, 138, 153, 180) or for the sum of 7 or 19 PCBs. *Immunological effects:* No evidence of immune system involvement, as expressed by a set of cytokines.	(354)
	PCB 44	0.013 (< 0.001–0.16)	0.0010	3.1 (< 0.2–35)	0.26		
	PCB 47	0.015 (0.0029–0.087)	0.0036	3.7 (0.6–18)	1.0		
	PCB 52	0.023 (0.001–0.20)	0.0037	5.5 (0.1–43)	1.0		
	PCB 56/60	0.036 (< 0.001–0.40)	0.0012	8.4 (< 0.1–115)	0.31		
	PCB 66	0.065 (0.0041–0.76)	0.0028	16 (1.1–220)	0.8		
	PCB 70	0.0087 (< 0.001–0.17)	0.0014	2.1 (< 0.2–41)	0.38		
	PCB 74	0.096 (0.014–0.56)	0.012	24 (3.0–160)	3.5		
	PCB 87	0.010 (< 0.001–0.076)	0.0012	0.92 (0.27–16)	0.30		
	PCB 95	0.028 (0.0018–0.19)	0.0024	6.9 (0.65–52)	0.70		
	PCB 99	0.053 (0.011–0.20)	0.018	13 (3.4–59)	5.2		
	PCB 101	0.038 (0.0044–0.32)	0.0055	9.3 (0.8–70)	1.6		
	PCB 105	0.034 (0.066–0.21) [d]	0.0061	8.4 (1.7–61)	1.8		
	PCB 110	0.028 (0.0002–0.24)	0.0025	6.9 (0.54–52)	0.71		
	PCB 118	0.11 (0.018–0.59)	0.033	28 (5.2–170)	9.4		
	PCB 138	0.46 (0.10–1.5)	0.21	110 (29–640)	59		
	PCB 153	0.51 (0.13–1.6)	0.29	130 (37–540)	84		
	PCB 180	0.35 (0.097–1.4)	0.24	87 (28–330)	70		
	PCB 182/187	0.086 (0.018–0.34)	0.041	16 (5.1–110)	11.8		
	Σ 7 PCBs	1.6 (0.40–4.9)	0.80	410 (120–1 800)	230		
	Σ 19 PCBs	2.3 (0.56–7.8)	0.90	580 (160–2 200)	260		

[a] Reported as total PCBs. The PCB pattern resembled Aroclor 1260.
[b] Background blood levels were determined by calculating the 95 % quantile in 2 941 randomly selected individuals without a history of exposure to the chemicals.
[c] The higher total serum values among the abatement workers were suggested by the authors to be secondary to historical occupational exposure.
[d] GM and range are incompatible but are stated like this in the reference.
GGT: γ-glutamyl transferase, GM: geometric mean, IL: interleukin, T_3: triiodothyronine, T_4: thyroxine, TSH: thyroid-stimulating hormone.

14. Evaluation of human health risks

14.1 Assessment of health risks

Polychlorinated biphenyls (PCBs) comprise 209 compounds (congeners) of which 12 are dioxin-like. Commercial PCBs are liquid mixtures consisting of ~ 70–100 congeners with the dioxin-like PCBs as minor or trace constituents. PCBs are non-volatile, although low-chlorinated congeners have a much higher vapour pressure than high-chlorinated. All PCBs are lipophilic and some are very persistent and accumulate in the food chain. Food of animal origin (e.g. fatty fish) is a main source of PCB exposure for the general population as well as for occupationally exposed. Nowadays, PCB production and use is banned or restricted worldwide, but occupational exposure to PCBs may still occur, e.g. during renovation work and handling of waste, and in PCB-contaminated buildings such as schools and offices.

Some studies from the Nordic countries indicate that total PCB plasma/serum concentrations in occupationally exposed are slightly elevated as compared to pre-exposure values or to control groups. The increase compared to controls may at least in part be due to historical occupational exposure. The PCB levels in workers are still within the range of those measured in the general population during the last two decades. For workers as a whole, the health risk is therefore expected to be similar to that for the general population. Subgroups at increased risk due to higher PCB loads may be identified among both occupationally exposed (insufficiently protected workers, workers exposed some decades ago) and the general population (heavy fish consumers, residents in PCB polluted areas).

The aim of this document was to focus on health effects from occupational PCB exposure of today. Therefore, mainly human and animal studies with low or relatively low PCB exposure levels were included.

In humans, the major important effects to consider from low-level PCB exposure are effects on reproduction and development and possibly cancer. However, data do not allow definite conclusions. A comparison between studies is complicated, e.g. because of differences in the number of PCB congeners measured and the presence of contaminants in technical PCB mixtures (dioxin-like substances such as PCDFs). It is also difficult to distinguish the impact of PCBs in relation to other environmental pollutants. The large animal data base indicates an overall LOAEL of 5 µg/kg bw/day in monkeys at oral administration, but does not allow the identification of a NOAEL.

The developing foetus and infant seem to be vulnerable to PCB exposure and there is a growing body of evidence from studies on the general population that PCBs may contribute to slight neurobehavioural alterations, including impairment of cognitive functions. In humans, also subtle immunological effects in infants and possibly reduced birth weights have been indicated. Animal data support these findings. Increased locomotor activity was indicated in 12-month old infants of monkeys given Aroclor 1248 at a dose corresponding to approximately 6.3 µg/kg bw/day before and during gestation and lactation. A learning deficit and neurobehavioural changes were suggested in monkeys dosed from birth to 20 weeks of

age with 7.5 µg/kg bw/day of a PCB mixture. Resorptions, foetal and post-partum death occurred in impregnated monkeys dosed with 5 µg/kg bw/day of Aroclor 1254 before and during gestation. Mild immunological effects in infant monkeys were shown from 5 µg/kg bw/day (dosing of dams only) and at 7.5 µg/kg bw/day (dosing of infants only) with different PCB mixtures.

No major impact of PCBs on human male fertility has been demonstrated, but some studies of the general population indicate that PCBs might contribute to adverse effects on sperm motility, although alternative explanations are possible. In monkeys, decreased spermatogenesis was seen in 1 of 4 males after exposure for one year to approximately 100 µg/kg bw/day of Aroclor 1248.

Subtle alterations in thyroid hormones have been reported in some, but not all, of the studies of the general population and no definite conclusions can be drawn. In rats, increased levels of thyroid hormones were observed after a 30-day exposure to Aroclor 1242 at 33 µg/kg bw/day, whereas long-time exposure to 90 µg/kg bw/day of Aroclor 1254 resulted in decreased levels.

Adverse dermal and ocular effects (including chloracne) have not been reported in PCB exposed subjects in the general population, except in poisoning incidents. Thus, in humans such effects seem to be related to high-dose exposure to PCBs and/or exposure to PCDFs. In contrast, dermal and ocular effects in monkeys are sensitive indicators of toxicity of the studied PCB mixtures and have been observed at 5 µg/kg bw/day of Aroclor 1254.

For diabetes, no firm conclusion can be drawn. PCBs have been associated with diabetes in a number of studies on the general population, but the possibility of a reverse causality or that both PCB levels and diabetes are independently related to fat turnover cannot be ruled out. No obvious support for a relationship between PCB exposure and diabetes was found in mortality studies of highly exposed occupational cohorts. On the other hand, mortality is a crude measure of diabetes.

Overall, the results of *in vitro* and *in vivo* genotoxicity studies indicate that technical PCB mixtures are not directly mutagenic, but indirect genotoxic mechanisms have been described.

Regarding cancer, results from epidemiological studies are conflicting and do not allow a definite conclusion. In some of the occupational studies, an association between PCB mixtures and increased risks for prostate cancer and possibly cancer of the liver and biliary tract, and for malignant melanoma is suggested. Several studies of the general population have indicated a positive relationship between PCB levels and risk of non-Hodgkin's lymphoma (NHL).

PCB mixtures are carcinogenic in animals and are known as tumour promotors. Mainly liver tumours are induced. Cancer has occurred only at PCB dose levels exceeding those inducing other effects. PCBs were classified as a carcinogen in Group 2A (probably carcinogenic to humans) by IARC in 1987 without distinction between dioxin-like and non-dioxin-like congeners. Recently, PCB 126 (the most potent of the dioxin-like PCBs) was classified by IARC as a human carcinogen in Group 1 on the basis of animal data and mechanistic information. PCB 126 was considered a complete carcinogen in experimental animals and cancer was induced predominantly in the liver and lung.

In addition to cancer, chloracne and effects on immune function, thyroid and liver have been linked to dioxin-like PCBs and other dioxin-like compounds, even though non-dioxin-like PCBs may also contribute to some of these effects. The effects of non-dioxin-like PCB congeners are less well known, although they occur in blood at much higher levels. Some data suggest that non-dioxin-like PCB congeners are important for the neurobehavioural effects seen in offspring.

14.2 Groups at extra risk

The foetus and new-born are especially vulnerable to PCBs. Among the effects that at least partly have been attributed to prenatal and postnatal PCB exposure are those affecting neurobehavioural functions and the immune system.

14.3 Scientific basis for an occupational exposure limit

Studies on health effects of occupational low-level PCB exposure are few, but as plasma/serum PCB levels in occupationally exposed seem to be in the same range as those of the general population, their health risks are presumably similar. Studies on the general population suggest that PCB mixtures may slightly affect sperm motility and possibly contribute to an increased risk for non-Hodgkin's lymphoma in adults. In offspring, PCB exposure may contribute to subtle developmental changes including effects on neurobehavioural functioning, immune system and, possibly, birth weights. No threshold levels can be estimated based on current knowledge. Co-exposure to other pollutants hampers interpretation of the data. However, many of the effects seen in humans have also been reported in animals.

In animals, the overall LOAEL at oral administration of PCB mixtures is 5 μg/kg bw/day at which ocular/dermal, immunological, reproductive and developmental effects were observed in monkeys. No animal NOAEL can be identified.

PCBs mixtures are carcinogenic in animals, although cancer occurred only at dose levels far in excess of the LOAELs for other effects. Mainly liver tumours were induced.

Overall, it may be suspected that any occupational exposure to PCBs increases the risk for adverse health effects. Elevated blood levels of non-dioxin-like PCBs due to occupational exposure can be assessed by measuring certain marker PCBs. The potential health risk of the dioxin-like PCBs can be estimated from the TEQ concentration for PCBs using the TEF approach.

15. Research needs

- Epidemiological studies in the general population relating PCB levels to various health outcomes (including thyroid function, cardiovascular disease, hypertension, diabetes and endocrine effects).
- Exposure measurements during work with suspected PCB exposure.
- Occupational studies addressing the importance of different exposure routes.

16. Summary

Lindell B. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 146. Polychlorinated biphenyls (PCBs).* Arbete och Hälsa 2012; 46(1):1-181.

Polychlorinated biphenyls (PCBs) are a class of 209 synthetic compounds (congeners), in which 1–10 chlorine atoms are attached to biphenyl in different combinations. PCBs are non-volatile, although low-chlorinated congeners have a much higher vapour pressure than high-chlorinated. All PCBs are lipophilic and some are very persistent. For environmental reasons, PCB production and use is nowadays banned or restricted worldwide. PCBs were produced as mixtures with very different compositions, consisting of ~ 70–100 congeners with dioxin-like PCBs as minor constituents. They were used e.g. as hydraulic oils, as cooling liquids in electrical equipment and in building materials including elastic sealants.

Food of animal origin (e.g. fatty fish) is the main source of environmental PCB exposure. Occupational exposure to PCBs may occur e.g. during renovation work and handling of waste but also in PCB-contaminated buildings such as schools and offices. Limited data indicate that occupationally exposed in the Nordic countries have slightly elevated total PCB plasma/serum levels as compared to pre-exposure values or to control groups. The increase compared to controls may at least in part be due to historical occupational exposure. The total PCB levels in workers are still within the range of those measured in the general population during the last two decades. The plasma/serum concentrations of certain PCB congeners can be used as markers of occupational exposure.

As total PCB plasma/serum levels in occupationally exposed seem to be in the same range as those of the general population, their health risks are presumably similar. Studies on the general population suggest that PCB mixtures may slightly affect sperm motility and possibly contribute to an increased risk for non-Hodgkin's lymphoma. In offspring, PCB exposure may contribute to subtle developmental changes including neurobehavioural effects (e.g. on cognition), effects on immune system, and, possibly, birth weight. Yet, co-exposure to other pollutants hampers interpretation of the data.

Many of the effects seen in humans have also been reported in animals. The effects of PCB mixtures in animals occurring at the lowest dose levels (5–7.5 µg/kg bw/day) are effects on reproduction (resorptions/foetal death) and development (e.g. neurobehavioural effects), immune system, skin/nails and eyelids. Thyroid effects and effects on male fertility have been reported at higher doses, and cancer only at much higher doses. Many of the effects have been attributed primarily to dioxin-like congeners. The most potent dioxin-like PCB congener, PCB 126, has been classified by IARC as a human carcinogen based on animal and mechanistic data. Some data suggest that the non-dioxin-like PCB congeners are important for the neurobehavioural effects in offspring.

Keywords: Aroclor, cancer, developmental, diabetes, fertility, immunotoxicity, non-Hodgkin's lymphoma, occupational exposure limit, PCB, polychlorinated biphenyls, reproductive, review, risk assessment, thyroid, toxicity

17. Summary in Swedish

Lindell B. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 146. Polychlorinated biphenyls (PCBs).* Arbete och Hälsa 2012; 46(1):1-181.

Polyklorerade bifenyler (PCB) är en ämnesgrupp som omfattar 209 syntetiska föreningar (kongener) bestående av en bifenyl med 1-10 kloratomer i olika kombinationer. De är icke flyktiga ämnen, men lågklorerade kongener har mycket högre ångtryck än högklorerade. Alla PCB-kongener är lipofila och vissa är mycket persistenta. Av miljöskäl är tillverkning och användning av PCB numera förbjuden eller begränsad världen över. De kommersiella PCB-blandningarna hade mycket varierande sammansättning och bestod av 70–100 PCB-kongener, varav dioxinlika kongener utgjorde en liten del. PCB användes t.ex. som hydrauloljor, kylvätskor i elektrisk utrustning samt i byggnadsmaterial, bl.a. fogmassor.

Animalisk föda (t.ex. fet fisk) utgör den största källan till omgivningsexponering för PCB. Yrkesmässig exponering för PCB kan förekomma t.ex. vid renoveringsarbeten och avfallshantering men också i PCB-kontaminerade byggnader som skolor och kontor. Begränsade data antyder att yrkesexponerade i de nordiska länderna har något förhöjda totala PCB-nivåer i plasma/serum jämfört med nivåer före aktuell exponering eller vid jämförelse med kontrollgrupper. Förhöjningen jämfört med kontroller kan åtminstone delvis bero på historisk yrkesmässig exponering. De totala PCB-halterna hos arbetare är dock i nivå med de som uppmätts hos allmänbefolkningen de senaste 20 åren. Halterna av vissa PCB-kongener i plasma/serum kan användas som markörer för yrkesmässig exponering.

Eftersom de totala PCB-nivåerna i plasma/serum hos yrkesexponerade tycks vara i samma storleksordning som hos befolkningen i övrigt är också hälsoriskerna troligen likartade. Studier på allmänbefolkningen antyder att PCB-blandningar kan påverka spermierörligheten något, möjligen bidra till en ökad risk för non-Hodgkins lymfom hos vuxna samt bidra till subtila utvecklingsförändringar, t.ex. påverkan på beteende, kognitiv förmåga, immunsystem och möjligen födelsevikt. Samtidig exponering för andra miljöföroreningar försvårar dock tolkningen av data.

Många av de effekter man sett hos människa har också observerats hos djur. De effekter av PCB-blandningar som setts vid lägst doser på djur (5–7,5 µg/kg kroppsvikt/dag) är effekter på reproduktion och utveckling (t.ex. missfall, beteende-/inlärningsstörningar), immunsystem, hud/naglar och ögonlock. Effekter på sköldkörtel och fertilitet hos handjur har setts vid högre doser och cancer endast vid mycket högre doser. Många effekter anses bero främst på dioxinlika kongener. Den mest potenta dioxinlika PCB-kongenen, PCB 126, har av IARC klassats som carcinogen för människa baserat på djurdata och mekanistiska data. Vissa data antyder att icke dioxinlika PCB-kongener har betydelse för beteende- och inlärningsstörningar hos avkomman.

Nyckelord: Aroclor, cancer, diabetes, fertilitet, hygieniskt gränsvärde, immunotoxicitet, non-Hodgkins lymfom, PCB, polyklorerade bifenyler, reproduktion, riskbedömning, sköldkörtel, toxicitet, utvecklingseffekter, översikt

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19. Data bases used in the search for literature

As a basis for this document we have used previously published reviews, primarily those by ATSDR (19), ICPS (188) and EFSA (98) published in 2000, 2003 and 2005, respectively. Other data were mainly obtained from the database PubMed. The initial literature search was performed in June 2005. Several updating searches were done, mainly with focus on human data, with a final search performed in November 2010.

Submitted for publication February 2, 2012.

Appendix 1. Occupational exposure limits

Occupational exposure limits (mg/m^3) for PCBs in different countries as TWAs.

Country (organisation)	All PCBs		With 42 % chlorine		With 54 % chlorine		Reference
	8-hour	STEL	8-hour	STEL	8-hour	STEL	
Denmark	0.01	0.02	-	-	-	-	(1)
Finland	0.5	1.5	-	-	-	-	(2)
Norway	0.01	0.03	-	-	-	-	(3)
Sweden	0.01	0.03	-	-	-	-	(4)
The Netherlands	-	-	-	-	-	-	(5)
Germany (DGF)	-	-	1.1	8.8	0.70	5.6	(6)
United Kingdom	0.1	-	-	-	-	-	(7)
US (ACGIH)	-	-	1	-	0.5	-	(8)
US (NIOSH)	0.001	-	0.001	-	0.001	-	(9)
US (OSHA)	-	-	1	-	0.5	-	(9)
EU	-	-	-	-	-	-	(10-12)

STEL: Short-term exposure limit (15-min TWA), TWA: time-weighted average (8 hours or for NIOSH up to 10 hours).

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12. *Indicative occupational exposure limit values.* Commission directives: 2009/161/EU of 17 December 2009. Official Journal of the European Union: 19.12.2009, L 338/87-89. Brussels: The European Commission, 2009.

Appendix 2. Previous NEG criteria documents

NEG criteria documents published in the scientific serial Arbete och Hälsa (Work and Health):

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4) *D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*

Substance/Agent	Arbete och Hälsa issue
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*
Manganese	1982:10
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
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Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Occupational exposure to chemicals and hearing impairment	2010;44(4)*
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*

Substance/Agent	Arbete och Hälsa issue
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

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