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Danish Health and Medicines Authority

HEALTH RISKS OF PCB IN THE INDOOR CLIMATE IN DENMARK – background for setting recommended action levels

2013

Background report prepared for DHMA by Nordic Institute of Sustainable Products and Environmental Chemistry and Toxicology

Health risks of PCB in the indoor climate in Denmark

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To supervise the project, the Health and Medicines Authority appointed the following working group: Specialized Medical Officer Lis Keiding, MD (chair), Head of Department, Public Health Medical Officer Henrik L. Hansen, MD, Professor and Toxicology Adviser Philippe Grandjean, MD, and Assistant Medical Officer Jeppe Nørgaard Rasmussen, MD (from 1 October 2013).
Comments and suggestions to the report as a whole were received from MD Birger Heinzow, State Social Services Agency, Kiel, Germany, and Adjunct Professor, School of Medicine, University of Notre Dame, Australia, and from SD Robert Herrick, Senior Lecturer, Harvard University, USA. Consultant, MD, DMSc Niels Ebbehøj, Bispebjerg Hospital, has commented on selected parts of the report, and comments on "4.6: Typical indoor air levels of PCB" were received from Professor, MSc, PhD Lars Gunnarsen, Danish Building Research Institute (SBi), Aalborg University.

Thanks to Niels Ebbehøj, Bispebjerg Hospital, Lars Gunnarsen, Aalborg University, and Vice President, MD, PhD Harald Meyer, Rockwool International A/S, former Bispebjerg Hospital, for permission to use some of their illustrations from the study in Farum.

Foreword

In 2009, the Danish Health and Medicines Authority recommended action levels for PCBs in indoor air. The reason was that considerable amounts of PCB had been found in buildings built or renovated during the period when PCB was used in sealants etc. in Denmark. In May 2011, the Danish government announced an action plan with many new initiatives for PCB in buildings, including a reassessment of the 2009 recommendations on action levels for indoor air. Thus, the Danish Health and Medicines Authority has taken the initiative to this report. The purpose is to collect and evaluate the most relevant part of the newly available research results on PCB exposures in indoor environments and the potential health effects of such exposures. The report is an important part of the basis for revising the recommended action levels from 2009.

Research Director Allan Astrup Jensen, Nordic Institute of Sustainable Products and Environmental Chemistry and Toxicology, is the author of the report and is hereby acknowledged for his thorough updating of scientific literature on the health risks of PCB. The author was guided by a Steering Committee, and comments and suggestions to the report as a whole were received from MD Birger Heinzow, State Social Services Agency, Kiel, Germany, and Adjunct Professor, School of Medicine, University of Notre Dame, Australia, and from SD Robert Herrick, Senior Lecturer, Harvard University, USA. Consultant, MD, DMSc Niels Ebbehøj, Bispebjerg Hospital, has commented on selected parts of the report, and comments on “4.6: Typical indoor air levels of PCB” were received from Professor, MSc, PhD Lars Gunnarsen, Danish Building Research Institute (SBi), Aalborg University.

The report is written in English as the Danish Health and Medicines Authority considers the content to be relevant to other countries with potential exposure problems for users of buildings from the period when PCB was used in buildings.

Since a final report on the mapping of PCB in materials and indoor air in a sample of Danish buildings, prepared by the Consortium Grontmij-Cowi, had not been published at the time of the final editing of this report, it has not been possible to refer to the report in this text.

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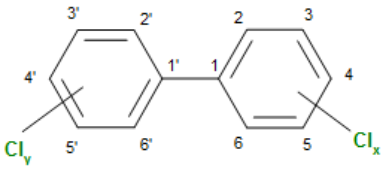
Dansk sammenfatning

1. PCBs egenskaber og anvendelser

PCB omfatter 209 forskellige isomere eller homologe chlorbiphenyler (congener), der har forskellige fysisk-kemiske egenskaber afhængigt af antal chlor-atomer og disses placering på biphenyl molekylets to sammenknyttede seksledede benzenringe.



Generel struktur af PCB

Handelsprodukterne, som ikke markedsføres mere, bestod af en blanding af omkring 100 enkelt-congener. Den samlede verdensproduktion af PCB har været på mere end 1 million tons. Det samlede forbrug af PCB i Danmark i perioden 1950-1983 er blevet skønnet til at andrage 1100-2000 tons.

PCB-handelsprodukterne var meget stabile, ikke-brændbare og elektrisk isolerende olier. På grund af disse nyttige egenskaber blev PCB brugt i forskelligt elektrisk udstyr og apparater, i hydraulikvæsker og i byggematerialer mv. Bygninger som blev opført i Danmark fra 1950'erne til omkring 1975, og hvor der blev anvendt PCB-holdige materialer, er blevet undersøgt. Det viste sig, at PCB stadig forekommer i fugematerialer i mere end 10 % af disse bygninger. PCB indholdet i fugematerialerne er sædvanligvis omkring 10 %, men kan være op til 70 %. Indholdet i malinger er sædvanligvis lavere.

PCB har en relativ lille flygtighed, der bliver endnu mindre med voksende chlor-indhold. Flygtigheden er imidlertid stor nok til, at små men målelige mængder af PCB konstant fordamper fra de PCB-holdige materialer og kan måles i luften. PCB i udeluften i byer er højere end på landet og højere om sommeren end om vinteren. I bygninger uden PCB er luftkoncentrationen mindre end 30 ng PCB/m^3, men i ikke-renoverede bygninger med PCB materialer kan koncentrationerne være 50-100 gange højere. Ved luftmålingerne bestemmes for det meste kun 6 eller 7 af de hyppigt forekommende markør-congener, og totalkoncentrationen af PCB fås ved at multiplicere summen med en faktor på 5.

2. Udsættelse for PCB i fødevarer og indeklima

Normalt indtager danskere dagligt det meste PCB fra fødevarer som fisk, kød og mejeriprodukter. Den gennemsnitslige indtagelse af PCB igennem maden i EU og i Danmark er henholdsvis 10-45 ng/kg kropsvægt og omkring 9 ng/kg kropsvægt.

Personer, som er udsat for PCB i indeklimaet, kan derudover indånde op til 10-100 gange mere PCB end det, der i forvejen indtages med maden. Der er imidlertid forskel på sammensætningen af PCB i luft og mad, idet de mest flygtige lavt chlorerede PCB congener dominerer i luften og de mindre flygtige højt chlorerede PCB congener dominerer i maden. Denne forskel komplicerer risikovurderingen.

PCB congener er opløselige i fedtstoffer (lipofile), og når vi indtager PCB vil det ophobes i kroppens fedtstoffer, hvorfra det kun medbrydes eller udskilles ganske langsomt med en halveringstid op til adskillige år.

Dette er forklaringen på, at beboere i nogle PCB forurenede lejligheder i Sverige havde 30 gange højere koncentration i blodet af den flygtige PCB28 forbindelse end beboere i lejligheder uden PCB. I en skole i Tyskland med PCB i fugemasserne havde elever 20 gange højere median koncentration af summen af PCB28, PCB52 og PCB101 i blodet end i ikke-forurenede skoler. En anden tysk skole, hvor forureningskilden var isoleringsmaterialer, der var flammehæmmet med mere chlorholdigt PCB, var koncentrationen af summen af PCB138, PCB153 and PCB180 i blodet fra de udsatte op til 18 gange højere end i en ikke-forurenet skole.

I undersøgelsen i Farum Midtpunkt viste det sig, at beboerne i de PCB forurenede lejligheder i gennemsnit havde omkring 4 gange mere PCB i blodet end beboere i ikke-forurenede lejligheder. Forskellen mellem de to grupper skyldtes primært, at beboerne i de forurenede boliger havde et højt indhold af lavt chloreret PCB i blodet, hvorimod beboerne i de ikke forurenede boliger stort set ikke havde lavt chloreret PCB i blodet. Jo længere beboerne havde boet i forurenede lejligheder des højere var koncentrationen af lavt-chloreret PCB. Beboerne i de forurenede lejligheder havde i gennemsnit boet der i 12 år.

3. Toksiske effekter af PCB i forsøgsdyr

Vedrørende giftighed skelner man mellem to grupper af PCB'er. De mest giftige har en såkaldt co-planar molekylstruktur svarende til den for dioxin og kaldes derfor dioxin-lignende PCB'er (DL-PCB). Disse congener andrager imidlertid kun en forsvindende del af det totale PCB i luft og mad, men da de er mere giftige end de andre ikke-dioxinlignende PCB'er (NDL-PCB) er de vigtige at tage i betragtning.

De fleste toksikologiske dyreundersøgelser af PCB er foretaget med handelsprodukterne, hvis sammensætning ikke svarer til den, som normalt ophobes i mennesker. Der er kun et begrænset antal undersøgelser af de enkelte PCB congener. Normalt optages PCB hurtigt og næsten fuldstændigt i mave-tarm kanalen, ved indånding og gennem huden. PCB er meget modstandsdygtigt overfor omdannelse i kroppen, men en meget lille del omdannes til de mere giftige hydroxy-PCB'er (OH-PCB).

PCB kan fremkalde toksiske effekter i diverse organer, og der er en betydelig forskel i dyrearters modtagelighed. Immunsystemet er blandt de mest følsomme organsystemer for PCB, og i forsøgsdyr forårsager PCB atrofi af brislen (thymus) og svækkelse af immunsystemet.

Hormonsystemet er også et vigtigt målorgan for PCB. Nogle af de lavt-chlorerede PCB'er og deres metabolitter har en svag østrogen effekt, mens de højt-chlorerede PCB'er primært er anti-østrogene. PCB nedsætter koncentrationen af skjoldbruskkirtelhormonet thyroxin i blodet ved at binde sig til et protein, der transporterer thyroxin rundt i kroppen. PCB kan ligeledes fremme udviklingen af overvægt og den dermed forbundne insulinresistens, hvorfor PCB kan være medvirkende årsag til udviklingen af type 2 diabetes.

I dyreforsøg fremkalder PCB en lang række skadelige effekter på frugtbarhed og formering, såsom nedsat sædkvalitet, ændret menstruationscyklus, en forøget forekomst af fostermisdannelser, færre unger per kuld, lavere fødselsvægt, mindre overlevelse og vægtforøgelse samt funktionsdygtighed for ungerne.

PCB kan skade udviklingen af nervesystemet og den effekt har vist sig at forekomme efter langtidsudsættelse for meget lave koncentrationer af de ikke-dioxinlignende (NDL) PCB'er, bl.a. PCB28. De forskellige PCB congener påvirker forskellige områder af hjernen. Af særlig interesse er at fritter (en slags

ilder) udsat for flygtige PCB'er i luften optager PCB gennem næsen, og derfor trænger ind i hjernen gennem lugtenerven.

Skønt PCB i sig selv ikke synes at være genotoksisk, så inducerer PCB leverenzymer, som kan ændre omsætningen af andre fremmedstoffer, så disse bliver genotoksiske. Fire PCB handelsprodukter har fremkaldt leverkræft i langtidsforsøg med rotter. De dioxinlignende PCB126 og PCB118 er kræftfremkaldende i forskellige organer i rotter, mens de ikke-dioxinlignende PCB 52 og PCB153 fremmer leverkræft i mus.

4. Effekter af PCB på mennesker

I forskellige grupper af PCB-eksponerede arbejdere er der rapporteret om øget dødelighed af modermærkekræft, hjerne- og tarmkræft. I en anden undersøgelse var dødeligheden af livmoder-, prostata- og mavekræft samt myelomatose (en form for blod/knoglekræft) stigende med skønnet kumulativ PCB eksponering.

En arbejdsgruppe nedsat af det internationale kræftforskningscenter (IARC) konkluderede i deres seneste evaluering fra februar 2013, at der var tilstrækkelig evidens for en kræftfremkaldende effekt i mennesker, og PCB, herunder såvel dioxin-lignende som ikke dioxin-lignende, blev derfor klassificeret som kræftfremkaldende i mennesker (Gruppe 1). Denne seneste vurdering af PCB medtog blandinger af congener, fordi den kræftfremkaldende effekt ikke syntes begrænset til et lille antal congener, og fordi menneskers udsættelse for PCB, om det er fra indeluften eller fra andre kilder, altid sker som blandinger af mange congener. Skønt IARC normalt ikke inkluderer kilde-egenskaber i sin vurdering, så præciseres det at den nye klassificering også gælder de vigtige udsættelser for PCB fra byggematerialer, dvs. også de lavklorerede former for PCB. Vurderingen er baseret på effekten af blandinger af PCB og det præciseres, at konklusionen er baseret på det forhold, at det på nuværende tidspunkt ikke er muligt at identificere, hvilke congener, der er af størst betydning.

Toksiske effekter i mennesker er også kendte fra masseforgiftninger som fx "Yusho"-ulykken i Japan i 1968, som ramte mere end 1800 mennesker med bl.a. alvorligt hududslæt og øget kræftrisiko til følge. Forgiftningen skyldtes at markedsført risolie ved et uheld under forarbejdningen var blevet forurenet med PCB. Men samtidigt var risolien også blevet forurenet med dioxin-lignende polychlorerede dibenzofuraner, så sundhedseffekterne skyldtes ikke kun PCB. I en senere lignende masseforgiftning, "YuCheng", i Taiwan blev der konstateret en tre gange forøget dødelighed af kronisk leversygdom, og risikoen for diabetes blandt kvinder var fordoblet. Udsatte børn havde dårligere kognitiv udvikling.

PCB kan påvirke udviklingen og funktionen af forplantningssystemet hos mennesker. Rapporterede effekter inkluderer: nedsat sædkvalitet, hæmning af fosterudviklingen og øget risiko for ufrivillig abort. Tilsyneladende er der en sammenhæng mellem PCB udsættelse og hormonforstyrrelser, så som nedsat niveau af kønshormoner i blodet og ændret funktion af skjoldbruskkirtlen.

Mange undersøgelser tyder på, at PCB kan fremme udviklingen af fedme i mennesker og medvirke til øget forekomst af overvægt. Desuden tyder adskillige undersøgelser på en sammenhæng mellem PCB udsættelse og ændringer i insulinomsætningen samt forekomsten af metabolisk syndrom der øger risikoen for udvikling af hjerte-kar sygdomme og diabetes. I en undersøgelse havde kvinder med de højeste PCB niveauer i blodet tre gange så stor risiko for type-2 diabetes. Risikoen for type-2 diabetes er særlig høj for

overvægtige personer, og de mest PCB udsatte overvægtige i Spanien havde da også ni gange forøget risiko for type-2 diabetes. En international videnskabelig workshop organiseret af de amerikanske sundhedsmyndigheder konkluderede fornyligt, at der var en forbindelse mellem PCB og øget risiko for type-2 diabetes, men at der ikke var tilstrækkelige data til at bevise en årsagssammenhæng.

Der er stigende evidens for, at PCB også i mennesker har en negativ påvirkning af immunsystemet gennem immunosuppression og immunsystem stimulering/inflammation. Udsættelse for PCB er forbundet med øget forekomst af luftvejsinfektioner, øreinfektioner, influenza og skoldkopper hos børn i skolealderen. Forøget PCB koncentration i blodet er ligeledes forbundet med lavere antistof respons ved barndommens rutine vaccinationer. I Slovakiet, hvor der er mange mennesker med særlig stor PCB udsættelse pga. en tidligere PCB produktion og stor industrianvendelse, fødte de mest PCB belastede mødre børn med nedsat størrelse af brislen.

Udviklingen af fostre og småbørn anses for at være særlig følsom overfor PCB's effekter, specielt udviklingen af nervesystemet og neuropsykologiske funktioner påvirkes. Endvidere kan der være en sammenhæng mellem PCB og udvikling af Parkinson's sygdom, idet koncentrationen af PCB153 var forhøjet i hjernevæv fra afdøde Parkinson patienter, og en gruppe kvindelige arbejdere med kraftig PCB udsættelse havde en øget risiko for at få denne sygdom.

Desuden er der undersøgelser, der tyder på at PCB udsættelse kan forårsage forhøjet blodtryk og forhøjet indhold af cholesterol i blodet og dannelse af atherosclerotiske belægninger og karsygdom.

5. Risikovurdering og udbedring

Verdenssundhedsorganisationen (WHO) har anbefalet en tolerabel daglig indtagelse (TDI) af ikke-dioxinlignende PCB på 20 ng PCB/kg kropsvægt. Denne værdi er baseret på den laveste observerede skadelige effekt (LOAEL) på 5 µg PCB/kg kropsvægt hos aber for et kommercielt PCB-produkt (Aroclor 1254).

En mindre del af den danske befolkning overskrider allerede denne tolerable indtagelse af PCB fra maden. EU Kommissionen har fastsat en tolerabel ugentlig indtagelse (TWI) på 14 pg dioxinækvivalenter/kg kropsvægt. Også for dioxin + dioxin-lignende PCB er der en mindre del af den danske befolkning, især børn, der indtager mere.

Anbefalede aktionsværdier for indendørs udsættelse for PCB blev først fastsat i Tyskland i 1996. Den laveste værdi for årlig middelværdi var 300 ng/m^3, og interventions værdien var 3000 ng/m^3 (3 µg/m^3). Den totale PCB koncentration blev beregnet som summen af de 6 markør-congener (PCB_6) multipliceret med en korrektionsfaktor på 5. Den toksikologiske baggrund dengang var en tolerabel daglig indtagelse (TDI) på 1-3 µg PCB/kg kropsvægt på baggrund af langtidsudsættelse hos rotter for en teknisk PCB blanding. Nyere undersøgelser tyder på, at der er skadelige effekter hos rotter ved udsættelse for 900 ng PCB/m^3 i luften og hos aber dagligt udsat for 5 µg PCB/kg kropsvægt.

PCB i fugemasser i bygninger kan migrere 30 mm ind i tilstødende materialer, såsom puds, beton og mursten. PCB i indeluften kan aflejres på alle overflader i rummet og på møbler og inventar. Sådanne kontaminerede overflader er sekundære og tertiære PCB kilder i indeklimaet.

Med hensyn til nedbringelse af PCB udsættelsen fra byggematerialer, har målinger i Danmark vist at hyppig støvsugning og anden rengøring kan nedbringe høje indendørs PCB-koncentrationer 2-3 gange, men en varig sænkning forudsætter løbende fortsættelse af den øgede rengøring. Hensigtsmæssig ventilation vil også nedsætte PCB i indeluften, men PCB i luften vil stige igen, når ventilationen ophører, fordi PCB fortsætter med at afdampe fra primære, sekundære og tertiære kilder.

Rengøring kombineret med ventilation er normalt ikke tilstrækkeligt til at bringe PCB i indeluften under 300 ng/m^3, hvis der er høje koncentrationer. Derfor kan det være nødvendigt at fjerne primære, sekundære og tertiære kilder og indkapsle eventuelle restforureninger bagefter. På den måde kan indendørs niveauerne af PCB nedsættes til under 100 ng/m^3.

English short summary

Polychlorinated biphenyls (PCBs) constitute 209 different chlorinated congeners with different physico-chemical properties depending on chlorine content and structure. More than 100 of these congeners were produced as part of commercial PCB mixtures, with a total World production in excess of 1 million tons. The total PCB use in Denmark in the period 1950-1983 has been estimated to 1100-2000 tons.

The PCB mixtures were very stable, inflammable, and electrically insulating. Due to their useful properties, PCBs have been used in electrical equipment, construction materials and for many other purposes. Some of the PCB congeners are particularly resistant to break-down, and routine PCB analyses usually focus on six or seven of the most abundant congeners, from which the total amount of PCB can be estimated. PCBs remain in caulking/sealing materials in more than 10% of the Danish buildings from the 1950s to about 1975. The PCB content in such material is usually about 10%, but can vary up to 70%. In paint the PCB concentration may be lower.

PCBs have relatively low volatility, especially at higher chlorine contents. Air concentrations are higher in urban than rural areas, and indoor levels are typically about 30-fold higher than those outdoors. Non-contaminated buildings typically have air levels less than 30 ng PCB/m^3 (measured as PCB_6 or PCB_7), while non-renovated contaminated buildings show concentrations that are 50-to-100 fold higher, i.e., higher than the existing limit of 100 ng PCB/m^3 for industrial air emissions.

Food is a main source of human PCB exposure, and the average daily intake via this pathway has been estimated to be 10-45 ng/kg body weight (bw) in the EU. The most recent Danish intake estimate is a mean daily intake from food of 9 ng/kg bw (maximum, 82 ng/kg bw). For an adult person weighing 60-70 kg, the order of magnitude for daily intake via food would be about 1 µg/day.

The EU established in 2012 action and maximum levels of dioxins and dioxin-like (DL) PCBs, and for non-dioxin-like (NDL) PCBs in foodstuffs. These limits were based on an extensive data base on toxicity risks. Along with more recent data, this information also relates to exposures via indoor air.

For comparison, at indoor air concentrations of 300-3 000 ng PCB/m^3, an adult may inhale about 20 m^3 air during 24 hours, thereby leading to an intake of approximately 6 000-60 000 ng PCB (as based on the standard PCB_6 measurement). Theoretically such intake exceeds the intake via food by 10-to-100-folds. However, major PCBs occurring in food include highly chlorinated congeners, much different from the pattern in air, thereby complicating comparative risk assessment. Nonetheless, the major congeners present in food also occur in indoor exposures that therefore serve as additional source of PCB exposure.

PCB congeners are soluble in fat (lipophilic) and will concentrate in the lipid phase of the body. Many congeners have elimination half-lives of several years, i.e., that they accumulate in the body and are excreted only very slowly.

Residents of contaminated apartments in Sweden showed higher blood concentrations of low-chlorination congeners, which have a higher vapor pressure, e.g., an increase of PCB28 in blood of 30-folds. In a German study of a PCB-contaminated school, the median blood concentrations of the sum of PCB52, PCB101 and PCB28 were 20 folds higher than in non-contaminated schools. However, in another school where the PCB

source was acoustic plates that had been flame-retarded with high chlorinated PCBs, the blood concentrations of PCB138, PCB153 and PCB180 were increased up to 18-folds.

In the Danish “Farum Midtpunkt” study, exposed dwellers had about 4-folds higher blood-PCB concentrations than the non-exposed: The longer the residence time, the higher the blood concentration of low-chlorinated PCBs.

Most animal toxicity data refer to commercial PCB mixtures, and fewer data exist for the single congeners. In general, PCBs are readily absorbed orally, dermally and by inhalation. PCBs are resistant to metabolism, but some may be metabolized into hydroxy-PCBs, which may contribute independent toxic effects. The most toxic PCBs have a “co-planar” conformation similar to that of dioxin and are thus called dioxin-like PCBs (DL-PCBs). They only constitute a small fraction of exposures from food and indoor air, but due to the higher toxicity, they should not be ignored. PCBs can elicit toxic effects from a variety of organs, and substantial species differences in sensitivity have been identified.

The immune system is among the most sensitive of all organ systems to PCBs. PCBs cause atrophy of the thymus gland and immunosuppression in laboratory animals. The endocrine system is also an important target for PCBs. Some lower-chlorinated PCB congeners and metabolites exhibit weak estrogenic effects, while higher-chlorinated PCBs are primarily anti-estrogenic. PCB mixtures and congeners effectively reduce circulating concentrations of the thyroid hormone. Some PCB metabolites bind to the protein that transports this hormone in the blood. PCBs may also trigger the development of obesity and of obesity-induced insulin resistance and hyperinsulinemia, thus suggesting possible induction of type-2 diabetes.

Reproductive toxicity in animals encompasses a range of adverse effects, such as decreased sperm counts, altered estrous/menstrual cycles, and greater incidence of malformations, fewer offspring per litter, lower birth weight, and less postnatal survival, weight gain, and functional levels of offspring.

Developmental neurotoxicity has emerged as a particularly vulnerable endpoint in chronic low-level PCB toxicity studies, and different NDL-PCBs seem to affect different targets in the brain. Of particular interest, upon inhalation exposure, ferrets absorb PCBs through the nose and the olfactory bulb, thereby penetrating directly into the brain.

Although PCB mixtures and congeners appear not to be genotoxic, PCBs may cause metabolic interference by converting non-genotoxic xenobiotics into genotoxic metabolites. Four commercial PCB mixtures have been tested in long-term studies in rats, and all caused liver tumors in females, Aroclor 1260 also in males. The DL-PCBs 126 and 118 cause cancer at several sites. NDL-PCBs 52 and 153 are promoters of liver tumors in mice.

In various groups of PCB-exposed workers, increased mortality from melanoma, brain cancer and intestinal cancer have been reported. Mortality of uterine cancer, prostate cancer, stomach cancer and multiple myeloma increased with estimated cumulative PCB exposure. In the most recent evaluation, in February 2013 the IARC working group concluded that there was sufficient evidence of carcinogenicity in humans, and PCBs were classified as carcinogenic to humans (Group 1). Dioxin-like PCBs were classified in Group 1 based on strong evidence for multiple mechanisms of carcinogenesis. The most recent evaluation of PCBs considered the mixture of congeners, since the carcinogenicity is not known to be limited to a small number of congeners, and because human exposures to PCBs, whether from indoor air or from other

sources, always involve mixtures of many congeners. Thus, although IARC does not consider source attribution in their evaluations, the current classification of PCBs also applies to exposures from construction materials, which may be one of the important sources of exposure.

Human toxicity is known from mass food poisoning events, such as Yusho in Japan that involved more than 1800 subjects. The poisoning was due to a commercial brand of rice oil that had been accidentally contaminated PCBs. However, the oil was also contaminated by dioxin-like polychlorinated dibenzofurans, thus making direct conclusions on PCB toxicity difficult. Among the long-term effects was an increased risk for cancer. In the similar YuCheng incident in Taiwan, the long-term effects included a 3-fold increased mortality from chronic liver disease, and the risk of diabetes among women was doubled. Exposed children had poorer cognitive development.

PCB may interfere with the development and function of the reproductive system in humans. Reported effects include decreased sperm motility, impaired fetal growth, and increased risk of pregnancy loss. Endocrine disruption is suggested by reduced sex hormone concentrations in serum. Increased prenatal PCB exposure has been linked to lower serum concentrations of both luteinizing hormone (LH) and testosterone (with an accompanying increase in sex-hormone-binding globulin), which may indicate a central effect. In addition, some studies suggest that PCBs or their hydroxy metabolites may interfere with thyroid gland functions.

Several studies suggest that PCBs may be obesogenic and contribute to the development of obesity in humans. Further, dozens of studies have linked PCB exposure to the metabolic syndrome, insulin insensitivity and changes in insulin secretion. One study reported that the women with the highest 20% of the blood-PCB concentrations had a 3-fold increased risk of type-2 diabetes. The risk may be greater in overweight subjects, e.g., in obese subjects in Spain, the group with the highest PCB concentrations had a 9-fold increased risk of diabetes. A recent expert workshop organized by the US Institutes of Health concluded that PCBs are associated with an increased risk of type-2 diabetes, although the data were not sufficient to establish causality.

Increasing evidence suggests that PCBs in humans can cause dysregulation of the immune system through immunosuppression and immune stimulation/inflammation. PCB exposure is associated with an increased incidence of respiratory infections, ear infections, influenza, and chicken pox in children at preschool age. Increased blood-PCB concentrations are also associated with lower antibody responses to routine childhood vaccinations. In Slovakia, mothers with an increased blood-PCB concentration gave birth to children with a reduced thymus volume.

The developing fetus and young infants are particularly vulnerable to PCB toxicity. PCB may affect neurodevelopment and neuropsychological functions in children. In addition, PCB may be a risk factor for the development of Parkinson’s disease. Thus, PCB-153 concentrations were elevated in human brain tissue from deceased Parkinson patients, and a cohort of heavily exposed female workers had increased risk for contracting this disease.

Among other likely or possible adverse effects in humans, blood-PCB concentrations have been linked to elevated blood pressure, elevated serum-cholesterol, formation of atherosclerotic plaques, and self-reported cardiovascular disease. Some of these effects may be associated with obesity.

The World Health Organization (WHO) has recommended a tolerable daily intake (TDI) of 20 ng PCB/kg bw which was derived from a Lowest Observed Adverse Effect Level (LOAEL) of 5 µg/kg bw in monkeys exposed to a commercial mixture of PCBs (Aroclor 1254). As a result of current dietary intake, this limit is exceeded by a small proportion of the Danish population. In regard to the DL-PCBs, the European Commission has established a tolerable weekly intake (TWI) of 14 pg TEQ/kg bw. Current dietary exposure in Denmark exceeds the limit for a small fraction of the population, mainly in children.

Specific action levels for 24-hour indoor exposure to PCBs were first established in Germany. The annual mean action value was 300 ng/m^3, and the intervention value was 3000 ng/m^3 (3 µg/m^3). The PCB concentration was calculated as PCB_6 multiplied with a correction factor of 5 to obtain the total-PCB concentration. At the time, the toxicological basis was a tolerable daily intake (TDI) for a technical PCB mixture of 1-3 µg PCB/kg bw/day derived from rat experiments. More recent studies have shown adverse effects in rats exposed to 900 ng PCB/m^3, and in monkeys at a daily intake of 5 µg PCB/kg bw/day.

In regard to mitigation of indoor PCB exposure from construction materials, measurements in Denmark have shown that frequent vacuuming, dusting and washing of floor, furniture, walls and ceilings can reduce high indoor air concentrations of PCB by 2-to-3-folds as long as the intervention is continued. Ventilation will also decrease air PCB concentrations temporarily, PCB concentration will increase again when the ventilation is turned off, as evaporation will continue from primary, secondary and tertiary sources. PCBs can migrate from sealing material 30 mm into adjacent materials, such as plaster, concrete and bricks, and PCBs can precipitate on furniture and textiles. Such contaminated materials constitute secondary PCB indoor pollution sources.

Cleaning combined with ventilation is not reported to be sufficient to bring indoor PCB concentrations below 300 ng/m^3 in settings, where the initial levels are high. Thus, in these cases it may be necessary to either remove or seal, or both, primary, secondary and tertiary sources, and enclose eventual residues. In such a way it has been possible to reduce indoor air PCB concentration to < 100 ng/m^3.

Indhold

1. Background

In April 2009 the Danish Environmental Protection Agency published a health assessment report about sealants in Danish buildings containing PCB.[1] A questionnaire survey, including 100 buildings, and a detailed chemical analysis of PCB in old sealant materials, indoor surface dust and indoor air in 10 buildings were performed to estimate the remaining mass of PCB in old sealants and to estimate the resulting human PCB exposure in buildings and its potential health effects. The total remaining mass of PCB in sealants in Danish buildings was estimated to be in the range of 6-21 tons. Concentrations of PCB (sum of up to 22 congeners) in indoor air ranged from below 30 to just above 1000 ng/m^3. Concentrations in indoor surface dust ranged from below 30 to just above 2000 ng/g. There was an association between PCB levels in sealant and indoor air. The PCBs measured in indoor air were mainly the lower chlorinated, non-dioxin-like congeners. The highest concentration measured was estimated to result in a daily exposure of about 70 fold below the no observed adverse effect level (NOAEL) in experimental animals. The congener composition in indoor dust resembled more commercial mixtures. The highest measured concentration was estimated to result in an exposure that was 3500 fold below the lowest observed adverse effect level (LOAEL) from animal tests. In that study only a very limited number of samples were analyzed for PCB, and it was not representative of the Danish situation. In connection with a renovation of a public school the Environmental Department of the Municipality of Copenhagen discovered a heavy PCB contamination in the removed building waste from the school. Following that more investigations of institutions and apartment buildings were initiated and more PCB contaminated buildings were discovered around the country and in Greenland. The authorities initiated a project on PCB in 1- and 2-family homes which in December 2009 summarized the present knowledge about PCB in buildings, nationally and internationally, as a basis for the future larger projects.[2]Also in 2009, the Danish Health and Medicines Authority recommended two action levels for PCB in indoor air.[3]

1. Levels >3000 ng/m^3 required immediate need for action.
2. Exposures to levels between 300 and 3000 ng/m^3 were considered to be a possible health risk and an action plan would be needed to bring levels down.

It was later specified that levels between 2000 and 3000 ng/m^3 required action before a year and lower levels within two years. In May 2011 the Danish government announced a new action plan for PCB in buildings with many new initiatives, including

- A more comprehensive survey of PCB in Danish buildings, building materials and indoor air
- Testing of methods for PCB renovation of buildings
- Better monitoring of renovation and demolition of buildings, and establishing limit values for PCB in building and construction waste
- A strengthen focus on occupational exposure to PCB

[1] Gunnarsen L, Larsen JC, Mayer P, Sebastian W. Sundhedsmæssig vurdering af PCB-holdige bygningsfuger. Orientering fra Miljøstyrelsen nr. 1, 2009. http://www2.mst.dk/common/Udgivramme/Frame.asp?http://www2.mst.dk/udgiv/publikationer/2009/978-87-7052-901-3/html/default.htm

[2] Jensen AA, Schleicher O, Sebastian W, Trap N, Zeuthen F. Forekomst af PCB i en- og tofamiliehuse. December 2009. http://www.ebst.dk/file/74259/pcb_enogtofamiliehuse.pdf; http://www.mst.dk/NR/rdonlyres/B281D13B-D668-43C2-8EBE-83F97105E83B/0/pcb_enogtofamiliehuse.pdf

[3] Bilag: Helbredsrisiko - PCB i byggematerialer (Sundhedsstyrelsen, februar 2011). http://www.sst.dk/~/media/Sundhed%20og%20forebyggelse/Indeklima%20og%20skimmelsvamp/bilag-risiko-endelig1.ashx

- Study of relative importance of PCB exposure from foodstuffs versus PCB exposure from indoor air
- Reassessment of the 2009 Action Limits for indoor air
- Various public information activities.

The aim of this report is to collect and assess the newly available information on PCB exposures in the indoor environment and the potential health effects of such exposures as a background for an eventual revision of the recommended action levels from 2009.

2. PCB chemistry, properties and uses

2.1 PCB structures, mixtures and congeners

PCB is the acronym for polychlorinated biphenyl. Polychlorinated biphenyls are a family of 209 homologue or isomeric chemical substances.[4] The individual substances are called PCB congeners. The structure of PCBs consist of two connected benzene rings (biphenyl), in which one or more of the 10 hydrogen atoms are substituted by chlorine. The general chemical structure of PCB is illustrated by the following structure formula (Figure 2.1):

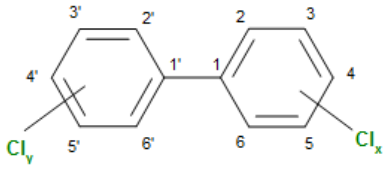


Figure 2.1: General structure of PCB.

The "x" and "y" each stands for a number from 0 to 5.The carbon atom positions are numbered 1 to 6 in the first ring and 1' to 6' in the other. The positions 2, 2', 6 and 6' are also called *ortho*-positions (*o*-); 3, 3', 5 and 5' are also called *meta*-positions (*m*-), and 4 and 4' are called *para*-positions (*p*-).

All the 209 PCB congeners do have a specific IUPAC number suggested the first time by one of the pioneers in PCB analysis: Karl Heinz Ballschmiter from University of Ulm, Germany.[5] The numbers, starting with PCB1 for 2-chlorobiphenyl, increase with the degree of chlorination but not necessarily with the appearance in a gas chromatogram.

This IUPAC number is often used as quick identification instead of the longer full systematic names, which are difficult to remember. For instance: PCB28 instead of 2,4,4'-trichlorobiphenyl, PCB52 instead of 2,2',5,5'-tetrachlorobiphenyl, PCB118 instead of 2,3',4,4',5- pentachlorobiphenyl, and PCB153 instead of 2,2',4,4',5,5'-hexachlorobiphenyl (see Figure 2.2):

[4] When no specific reference is mentioned, information is from general reviews such as:
- Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.
- IPCS Environmental Health Criteria 140 Polychlorinated biphenyls and terphenyls (second edition). Geneva: WHO, 1993.
- Toxicological Profile for Polychlorinated Biphenyls. Atlanta: ATSDR, November 2000.

[5] Ballschmiter K, Zell M. Analysis of polychlorinated biphenyls (PCB) by glass capillary gas chromatography. Fresenius Z Anal Chem 1980; 302: 20-31.

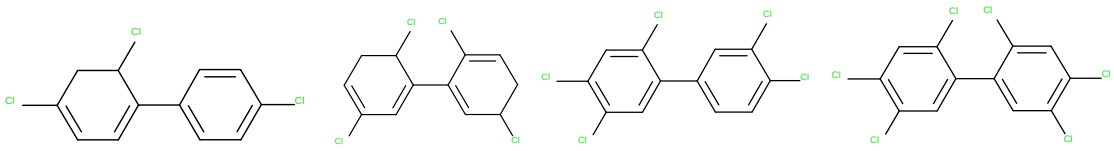


Figure 2.2: PCB28, PCB52, PCB118 and PCB153.

A few congeners without chlorine substitution in 2-, 2'-, 6- and 6'- positions (*ortho*-positions) have a co-planar conformation (non-*ortho*-PCBs). Although there is possibility of free rotation around the bond between the rings, the preferred conformation is planar as the fixed for dioxins and dibenzofurans. These non-*ortho*-substituted PCBs with at least 4 chlorine atoms are called dioxin-like (DL) PCBs. Similarly to dioxins DL-PCBs bind to the Aryl Hydrocarbon Receptor (AhR), and thus they do have similar toxicological mechanism (see later).[6] The most potent dioxin-like PCBs, which has chlorine substitution in both *para*-positions (4- and 4'-) and no *ortho*-substitution (2,2',6,6'), are PCB77, PCB81, PCB126 and PCB169 (see Figure 2.3):

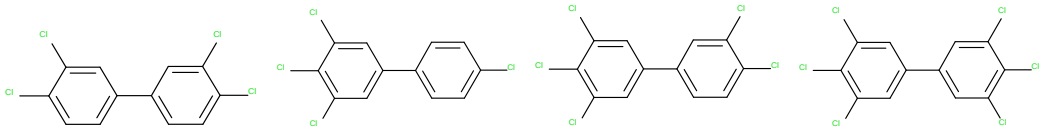


Figure 2.3: PCB77, PCB81, PCB 126 and PCB169.

The toxicities of the dioxin-like PCBs are expressed in Toxicity Equivalent Factors (TEFs) relative to TCDD but the potencies of the PCB congeners are lower than most of the dioxin congeners. On the other hand exposures to the PCBs are normally higher than to dioxins, so co-planar PCBs mean a lot in the total picture of for example food exposure to dioxin equivalents. The most toxic and common co-planar PCBs are PCB77, PCB81, PCB126, and PCB169.Some mono-*ortho*-substituted PCBs also have a dioxin-like toxicity but much weaker. They are: PCB105, PCB114, PCB118, PCB123, PCB156, PCB157, PCB167, and PCB189. The WHO Toxic Equivalency Factors for dioxin-like PCBs are shown in Table 2.1: [7]

[6] Kafafi SA, Afeefy HY, Ali AH, Said HK, Kafafi AG. Binding of polychlorinated biphenyls to the aryl hydrocarbon receptor. Environ Health Perspect 1993; 101: 422-428.

[7] Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds. Toxicol Sci 2006; 93: 223-241.

Table 2.1: The WHO Toxic Equivalency Factors for PCBs (van den Berg *et al.* 2006).

Compound	WHO 1998 TEF	WHO 2005 TEF
2,3,7,8-TCDD	1	1
non-ortho substituted PCBs		
PCB 77	0.0001	0.0001
PCB 81	0.0001	0.0003
PCB 126	0.1	0.1
PCB 169	0.01	0.03
mono-ortho substituted PCBs		
PCB 105	0.0001	0.00003
PCB 114	0.0005	0.00003
PCB 118	0.0001	0.00003
PCB 123	0.0001	0.00003
PCB 156	0.0005	0.00003
PCB 157	0.0005	0.00003
PCB 167	0.00001	0.00003
PCB 189	0.0001	0.00003

The rest of the *ortho*-substituted PCB congeners are the non-dioxin-like PCBs (NDL-PCBs) that have other toxicity mechanisms. If all four *ortho*-positions are occupied by chlorine the rotation around the biphenyl bond is totally hindered. Such congeners may have an asymmetric carbon atom and be chiral compounds with two optical isomers (enantiomers, mirrors).

2.2 Historical production

Initially, PCB was synthesized in 1864 but first introduced into commerce in 1927 in the USA by the Alabama-based Anniston Ordinance Company. In 1935 Monsanto took over the plant.[8] At that time PCB was considered relatively harmless and without significant toxicity but in the 1930s and the 1940s sporadic reports about toxicity were published in the literature of industrial medicine.[9] The main PCB producer from 1930 to 1977 was Monsanto Company with factories in the USA and United Kingdom. Its PCB production peaked in 1970 with about 33 000 tons a year. The total accumulated sale of PCB in the USA has been estimated to about 500.000 tons and in the whole World to around 1 million tons.[10] More detailed production figures have been published later.[11] PCB was manufactured by an industrial process with chlorination of biphenyl in the presence of iron catalysts (See Figure 2.4):

[8] http://www.foxriverwatch.com/monsanto2a_pcb_pcbs.html
[9] For example: Drinker CK, Warren MF, Bennet GA. The Problem of Possible Systemic Effects from Certain Chlorinated Hydrocarbons. J Industr Hyg Toxicol 1937; 19: 283-311.
[10] The hazards to health and ecological effects of persistent substances in the environment – polychlorinated biphenyls. Copenhagen: WHO Regional office for Europe, 1975.
[11] Brevik K, Sweetman A, Pacyna JM, Jones KC. Towards a global historical emission inventory for selected PCB congeners — A mass balance approach 3. An update. Science Total Environment 2007; 377: 296–307.

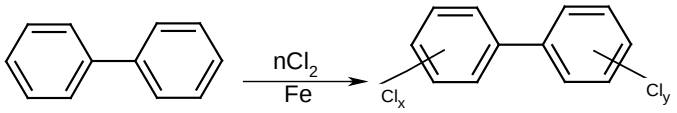


Figure 2.4: Synthesis method of PCB.

Depending on process conditions technical products consisting of complex mixtures of many PCB congeners were produced with a degree of chlorination varying between 21% and 70% by weight. At the chlorination process the first chlorine atom will practically always enter the biphenyl molecule in the *ortho*- and *para*-positions, so these positions will always be substituted. The second chlorine atom will usually enter the *ortho*- and *para*-position to the first chlorine substituted.

The produced technical PCB products were heavy, chemical stable, high-boiling and inflammable oils with low vapor pressures. These oils were soluble in organic solvents but almost insoluble in water. They were stable to and conducted heat but were electric insulating. In addition, these technical mixtures contained ppm impurities of the dioxin-like polychlorinated dibenzofurans (PCDFs), polychlorinated naphthalenes (PCNs), polychlorinated terphenyls (PCTs) with 3 connected chlorinated benzene rings, and polychlorinated quaterphenyls (PCQ) with four connected chlorinated benzene rings. The commercial mixtures were produced by several companies in various countries under many trade names and numbers. The most notable are shown in Table 2.2: [12]

Table 2.2: Some commercial PCB products (de Voogt and Brinkman 1989).

Trade name	**Company**	**Country**	**Average number of chlorine atoms and chlorine %**									
			2.5	1.25	2	3	4	5	6-6.3	6.8	8.7	9.5
			41.5%	21%	32-33%	40-42%	48%	52-54%	60%	62%	68%	70%
Aroclor	Monsanto	USA/UK	1016	1221	1232	1242	1248	1254	1260	1262	1268	1270
Clophen	Bayer	Germany				A30	A40	A50	A60			
Kanechlor	Kanegafuchi	Japan			200	300	400	500	600			
Phenoclor	Prodelec	France				DP3	DP4	DP5	DP6			
Fenclor	Caffaro	Italy				42		54	64		70	

Although the chlorine content may be the same, the exact congener composition of commercial formulations varies from producer to producer and from batch to batch. Not all of the 209 congeners are formed during the technical chlorination processes of biphenyl, only 50-70 different congeners are likely to occur in significant amounts in each of the various commercial products and in total about 130 congeners. In regard to the marketed Aroclor products the contents of the most abundant congeners are listed below in Table 2.3: [13]

[12] De Voogt P, Brinkman UATh. Production, properties and usage of polychlorinated biphenyls. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.
[13] Toxicological profile for polychlorinated biphenyls. Atlanta: ATSDR, November 2000.

Table2.3: Compositions (weight %) of PCB congeners in various Aroclor mixtures (ATSDR 2000).

PCB No.	PCB type	Aroclor			
		1242	**1248**	**1254**	**1260**
4		3	0.3	0.04	0.02
8	mono-*ortho*	**7**	0.8	0.1	0.04
16		3	1	0.05	0.01
17		3	1	0.05	0.01
18		**9**	**4**	0.2	0.05
22	mono-*ortho*	3	1.3	0.03	0.01
28	mono-*ortho*, DIN	**7**	**4**	0.2	0.03
31	mono-*ortho*	**7**	**5**	0.2	0.04
33	mono-*ortho*	**5**	2	0.1	0.03
44		**4**	**6**	1.5	0.03
49		3	4	0.5	0.01
52	DIN	**4**	**6**	1-5	0.2
66	mono-*ortho*	3	**6**	2	0.02
70	mono-*ortho*	**4**	**7**	**3-7**	0.04
74	mono-*ortho*	2	3	1.5	0.05
77	non-*ortho*	0.3	0.4	0.2	nd
81	non-*ortho*	0.01	0.01	nd	nd
99		0.5	1.5	**4**	0.04
101	DIN	0.7	2	**5-8**	**3**
105	mono-*ortho*	0.5	1.6	**3-7**	0.2
110		0.8	**3**	**9**	1.3
114	mono-*ortho*	0.04	0.1	0.5	nd
118	mono-*ortho*	0.7	2.3	**7-14**	0.5
123	mono-*ortho*	0.03	0.07	0.2	nd
126	non-*ortho*	nd	nd	0.02	0
138	DIN	0.1	0.4	**6**	**7**
153	DIN	0.06	0.2	3.5	**9**
156	mono-*ortho*	0.01	0.06	1	0.5
157	mono-*ortho*	nd	0.01	0.2	0.02
167	mono-*ortho*	nd	0.01	0.3	0.2
169	non-*ortho*	nd	nd	nd	nd
170		nd	0.08	0.4	**4**
178		nd	0.03	0.03	0.8
180	DIN	nd	0.2	0.5	**11**
182		nd	nd	nd	nd
183		nd	0.06	0.1	**2.4**
187		nd	0.09	0.2	**5.4**
189	mono-*ortho*	nd	nd	0.01	0.1
190		nd	nd	0.06	0.8
194		nd	nd	0.01	**2**

nd = non detected; bold for most abundant congeners

Table 2.3 illustrates that the lesser chlorinated products have a relatively high content of the lower chlorinated PCBs, among which only PCB28 and PCB52 are commonly quantified in air and blood samples.

The most quantified NDL-PCBs are PCB28, PCB52, PCB101, PCB138, PCB153, and PCB180, often called DIN congeners.[14] This congener mix was originally suggested by some German scientists for analysing PCB in

[14] DIN is the German standardization organization which used this congener selection for their early standards.

foodstuff of animal origin.[15] Later this method became more generally used in the EU for environmental - and food samples, sometimes with dioxin-like PCB118 included.

The approximate concentrations (weight %) of PCB_6 and PCB_7 determined by GC-MS in some important commercial mixtures are shown in Table 2.4.

Table 2.4: Concentrations (weight %) of the major PCB congeners in selected commercial mixtures.

PCB congener	Clophen[16]				Aroclor[17]			
	A30	A40	A50	A60	1242	1248	1254	1260
PCB28	12	3.6	0.05	0,02	7.1	5.5	0.1	0.07
PCB52	2.3	7.9	5	0.5	3.5	5.6	4.8	0.3
PCB101	0.4	2.4	8.9	5.3	0.8	2.5	9.7	2.8
PCB118	0.3	2.2	9.1	1.4	0.6	1.7	6.9	0.6
PCB138	0.1	0.4	6.6	12	0.06	0.2	7	8.3
PCB153	0.1	0,3	3.9	13	0.2	4.6	9.5	6.4
PCB180	0.01	0.1	0.4	8.1	0.01	0.4	1	13
PCB_6	14.9	14.7	24.9	38.9	11.7	18.8	32.1	30.9
PCB_7	15.2	16.9	34.0	40.3	12,3	20.5	39.0	31.5
Diff. in %	2.0	15.0	36.6	3.6	5.1	9.0	21.5	1.9

As seen the concentrations of PCB_6 and PCB_7 depend both on the producer and the chlorine content. The differences between using these two set of congeners are especially large for mixtures, for which the chlorine content is about 50%. It is also clear from the table that these 6-7 indicator congeners only correspond to 15-40% of the total PCB concentrations.

The total PCB content in a sample can be estimated by adding the results for de single congeners and multiplying the sum (PCB_{6-7}) with a correction factor of 2 to 5, depending on sample type. In Table 2.5 some calculated correction factors are given:

Table 2.5: Correction factors for quantification of PCB based on indicator PCBs.

	Clophen				Aroclor				Mean	Min	Max
	A30	A40	A50	A60	1242	1248	1254	1260			
PCB_6	6.7	6.8	4.0	2.6	8.6	5.3	3.1	3.2	5.0	2.6	8.6
PCB_7	6.6	5.9	2.9	2.5	8.1	4.9	2.6	3.2	4.6	2.5	8.1

For PCB_6 the average correction factor generally has been estimated to five, and this value has been the most often recommended correction factor for both PCB_6 and PCB_7 in standard methods and regulations. For instance, the German "Länderarbeitsgemeinschaft Abfall (LAGA)" recommended this factor 5 for solid and liquid waste.[18]

[15] Beck H, Mathar W. Zur Bestimmung von PCB in Lebensmitteln. Tätigkeitsbericht 1983, Bundesgesundheitsamt. München: MMV Medizinverlag, 1983.
[16] Takasuga T, Senthilkumar K, Matsumura T, Shiozaki K, Sakai S-I. Isotope dilution analysis of polychlorinated biphenyls (PCBs) in transformer oil and global commercial PCB formulations by high resolution gas chromatography-high resolution mass spectrometry. Chemosphere 2006; 62: 469-484.
[17] Schulz DE, Petrick G, Duinker JC. Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography-electron capture detector. Environ Sci Technol 1989; 23: 852-859.
[18] LAGA-Merkblatt: Entsorgung von PCB-haltigen Reststoffen und Abfällen 8375. Berlin: Erich Schmidt Verlag, 1998.

In some human and environmental studies only the most persistent PCB congener (PCB-153)was quantified as an indicator of PCB, however, in other studies such as the "Farum Midtpunkt" investigation up to 27 PCB congeners were analyzed and quantified in the apartments, including PCB66, PCB74, PCB99, PCB170, PCB178, PCB182, PCB183, PCB187, and PCB190.[19] It is unclear how large a part these 27 congeners are of the total PCB.

2.3 Physical-chemical properties

Although the PCB congeners do have many similarities, they have different chemical-, physical- and toxicological properties.

All PCB mixtures and congeners are stable, inert, inflammable, electrically insulating and good conductors of heat. In general, among the PCB mixtures and congeners the melting points increase with increasing molecular mass (chlorine content). There may, however, be some irregularities among isomers. The technical mixtures are oils, and most of the pure congeners with up to 3-4 chlorine are liquids/oils, and the pure higher congeners are solids. PCB mixtures and congeners have generally a very low volatility, and it decreases in general with increasing chlorine content.

In addition, PCB mixtures and congeners are poorly soluble in water with increasing chlorine content. The water solubility's of Aroclor's were determined to be in the range of 0.002-0.42 ng/L. The water solubility's of the single congeners PCB28, PCB52, PCB101 and PCB153 specifically have been estimated to 0.085-0.266 ng/L, 0.006-0.11 ng/L, 0.004-0.03 ng/L and 0.001-0.01 ng/L, respectively. A selection of vapor pressures and water solubility's of Aroclor's are shown in Table 2.6:

Table 2.6: Vapor pressure and water solubility of Aroclors (IPCS 1993).

Aroclor	Vapor pressure at 25°C		Water solubility at 25°C
	torr	Pa (converted)*	mg/L
1016	4.0×10^{-4}	0.053	0.42
1221	6.7×10^{-3}	0.89	0.59 (at 24°C)
1232	4.1×10^{-3}	0.55	0.45
1242	4.1×10^{-3}	0.55	0.24
1248	4.9×10^{-4}	0.0065	0.054
1254	7.7×10^{-5}	0.01	0.021
1260	4.0×10^{-5}	0,0051	0.0027

*1 torr = 133.3 Pa

In contrast, its lipophilicity expressed by the octanol-water partition coefficient (Log K_{ow}) increases with chlorine content.

The general CAS number for "PCB" is 1336-36-3. In Table 2.7 some CAS numbers, IUPAC numbers, systematic names, molecular masses, melting points, vapor pressures and partition coefficients (Log K_{ow}) are shown for some selected PCB-congeners:

[19] PCB eksponering i Farum Midtpunkt – måling i boliger og blod. København: Sundhedsstyrelsen, januar 2012.

Table 2.7: Properties of some selected PCB congeners.

CAS no.	IUPAC no.	Name	Mole-cular mass	Melting point (°C)[20]	Vapor pressure at 25°C Pa[21, 22]	Partition coefficient at 25oC (Log K_{ow})[23]
2050-68-2	15	4,4'-Dichlorobiphenyl	223.1		7.3×10^{-2}	5.23
7012-37-5	28	2,4,4'-Trichlorobiphenyl	257.54	58-59	3.4×10^{-2}	5.67
15862-07-4	29	2,4,5-Trichlorobiphenyl	257.54		4.5×10^{-2}	
35693-92-6	30	2,4,6-Trichlorobiphenyl	257.54		9.7×10^{-2}	
16606-02-3	31	2,4',5-Trichlorobiphenyl	257.54		3.5×10^{-2}	
38444-86-9	33	2,3',4'-Trichlorobiphenyl	257.54		2.6×10^{-2}	
41464-39-5	44	2,2',3,5'-Tetrachlorobiphenyl	291.99		1.3×10^{-2}	
2437-79-8	47	2,2',4,4'-Tetrachlorobiphenyl	291.99		1.5×10^{-2}	
35693-99-3	52	2,2',5,5'-Tetrachlorobiphenyl	291.99	85.5-86.5	1.6×10^{-2}	5.84
32690-93-0	74	2,4,4',5-Tetrachlorobiphenyl	291.99	127-129		6.20
32598-13-3	77	3,3',4,4'-Tetrachlorobiphenyl	291.99	180-181	2.2×10^{-3}	6.36
70362-50-4	81	3,4,4',5-Tetrachlorobiphenyl	291.99	160-163		6.36
38380-01-1	99	2,2',4,4',5-Pentachlorobiphenyl	326.43	59-60	2.9×10^{-3}	6.39
37680-73-2	101	2,2',4,5,5'-Pentachlorobiphenyl	326.43	78-79	3.4×10^{-3}	6.38
32598-14-4	105	2,3,3',4,4'-Pentachlorobiphenyl	326.43	117	8.7×10^{-4}	6.65
74472-37-0	114	2,3,4,4',5-Pentachlorobiphenyl	326.43	98-99		6.65
31508-00-6	118	2,3',4,4',5-Pentachlorobiphenyl	326.43	111-113	1.2×10^{-3}	6.74
65510-44-3	123	2',3,4,4',5-Pentachlorobiphenyl	326.43	134-135		6.74
57465-28-8	126	3,3',4,4',5-Pentachlorobiphenyl	326.43	160-161	4.9×10^{-4}	6.89
35065-28-2	138	2,2',3,4,4',5'-Hexachlorobiphenyl	360.88	79-80	5.1×10^{-4}	6.83
35065-27-1	153	2,2',4,4',5,5'-Hexachlorobiphenyl	360.88	102-103.5	6.8×10^{-4}	6.92
38380-08-4	156	2,3,3',4,4',5-Hexachlorobiphenyl	360.88	129.5-131	$2,2 \times 10^{-4}$	7.18
69782-90-7	157	2,3,3',4,4',5'-Hexachlorobiphenyl	360.88	161-162		7.18
52663-72-6	167	2,3',4,4',5,5'-Hexachlorobiphenyl	360.88	125-127		7,27
32774-16-6	169	3,3',4,4',5,5'-Hexachlorobiphenyl	360.88	208-210		7,42
35065-30-6	170	2,2',3,3',4,4',5-Heptachlorobiphenyl	395.32	137	8.1×10^{-5}	7.27
35065-29-3	180	2,2',3,4,4',5,5'-Heptachlorobiphenyl	395.32	112.5-114	1.3×10^{-4}	7.36
52663-68-0	187	2,2',3,4'5,5',6-Heptachlorobiphenyl	395.32	104-105	3.2×10^{-4}	7.17
39635-31-9	189	2,3,3',4,4',5,5'-Heptachlorobiphenyl	395.32	162-163		7,71
35694-08-7	194	2,2',3,3',4,4',5,5'-Octachlorobiphenyl	429.77	155-157		7,80

2.4 Previous use pattern

PCBs were used in an extreme variety of industrial and consumer applications. The The World Health Organization categorized the uses as *completely closed*, *nominally closed* and *open-ended* (IPCS, 1993).

These PCB uses included:

a) Completely closed systems:
   - Electrical transformers;
   - Electrical capacitors (including small fluorescent lighting ballasts);

[20] Bolgar M, Cunningham J, Cooper R, Kozloski R, Hubball J, Miller DP, Crone T, Kimball H, Janooby A, Miller B, Fairless B. Physical, spectral and chromatographic properties of all 209 individual PCB congeners. Chemosphere 1995; 31: 2687-2705.
[21] Shiu WY, Mackay D. A Critical review of aqueous solubilities, vapor pressures, Henry's Law Constants and octanol-water partition coefficients of the polychlorinated biphenyls. J Phys Chem Ref Data 1986; 15: 911-929.
[22] Falconer RL, Bidleman TF. Vapor pressures and predicted particle/gas distributions of polychlorinated biphenyl congeners as functions of temperature and ortho-chlorine substitution. Atmos Environ 1994; 28: 547-554.
[23] Hawker DW, Connell DW. Octanol-water partition coefficients of polychlorinated biphenyl congeners. Environ Sci Technol 1988; 22: 382-387.

- Electrical switches, relays and other;
- Electrical cables;
- Electric motors and magnets (very small amounts);

b) Nominally closed systems:
   - Hydraulic systems e.g. in underground mining equipment;
   - Heat transfer systems (heaters, heat exchangers);

c) Open-ended systems:
   - Plasticizer in polyvinyl chloride, neoprene and other artificial rubbers;
   - Ingredient in paint and other coatings;
   - Ingredient in ink and carbonless copy paper;
   - Ingredient in adhesives;
   - Pesticide extender;
   - Ingredient in lubricants, sealants and caulking material;
   - Fire retardant in fabrics, carpets, roof plates, polyurethane foam, etc.;
   - Lubricants (microscope oils, brake linings, cutting oils, other lubricants).
   - Decachlorobiphenyl (PCB209) was specifically used as filler for investment casting waxes.

In capacitors, the PCB products used were e.g. Aroclor 1016, 1221, 1242 and 1254. PCB-capacitors were produced in Denmark from 1960 to 1981.[24]

In transformers, the higher chlorinated Aroclor 1254 and 1260 were used in combination with 30-70% chlorobenzenes with the trade name Askarel®.

Advantages of PCB transformers included the inflammability of PCB that made it possible to build lighter and more compact transformers, thus saving weight and space, as they did not need to be placed in separate buildings. Such equipment was also easier to transport to remote places, and because PCBs better resisted cold and rough climates, PCB products and materials were frequently used in Greenland, Svalbard and other Arctic areas.[25]

Although a PCB transformer in principle cannot burn, it can overheat and explode. Therefore, when PCB-transformers were in burnings building, they sometimes exploded, and the chlorinated chemicals inside the transformer were released with smoke and soot, partly transformed into chlorinated dibenzofurans (PCDFs) and dioxins. Many such incidences around the world have exposed firefighters as well as contaminating buildings and their surroundings.

In the middle of 1970s OECD recommended the member countries to stop *open* uses of PCB. In Denmark all open applications of PCB and polychlorinated terphenyls (PCT) were banned in 1976.[26]

[24] Hansen E, Grove A. PCB/PCT-forurening. En udredning om forbrug, forurening og transportveje for PCB og PCT i Danmark. København: Miljøstyrelsen, 1983.
[25] AMAP Assessment 2002: Persistent Organic Pollutants in the Arctic. Oslo: AMAP, 2004.
[26] Miljøministeriets bekendtgørelse nr. 18 af 15. januar 1976 om begrænsninger i indførsel og anvendelse af PCB og PCT og Miljøministeriets bekendtgørelse nr. 572 af 26. november 1976 om ændring af og om ikrafttræden af bekendtgørelse om begrænsninger i indførsel og anvendelse af PCB og PCT.

It has been estimated that the consumption of PCB in electrical appliances and electronics in Denmark in the years 1950-83 was 600-1200 tons. In the beginning of the 1980s there were about 50.000 transformers and 8 million small capacitors with PCB still in use in Denmark.[27] In Table 2.8 the estimated PCB consumption in Denmark is shown:

Table 2.8: PCB consumption in Denmark, 1950-1983 (Hansen and Grove 1983).

USE AREA	TONS
Transformers and condensers	650-1200
Plasticizer in paint, caulking and sealing	300-500
Other industrial uses	150-300
In total	**1100-2000**

Later from November 1986 all new open or closed uses of PCB were banned in Denmark.[28] Larger capacitors and transformers with PCB were, however, allowed to be used until 1st January 1995, and small capacitors and transformer were allowed to be used the rest of their lifetime.

In 1998 a new Danish regulation based on an EU Directive from 1996 was introduced extending the larger equipment a lifetime until 1st January 2000.[29] However, according to a Danish EPA report from 2000 PCB-apparatus had already been phased-out by all Danish enterprises, previously using such equipment.[30]

3. PCB in the environment

Nowadays, PCB is detected as a trace pollutant everywhere in the global environment. Probably, this contamination began locally before the Second World War and increased and became wide-spread with the increasing industrial usage of PCB. However, it was first in 1966 PCB accumulation in nature and food chains became known to scientists and the public. It has been estimated that by the end of 2005 up to 12% of the produced PCB had been emitted into the air mainly from open uses.[31]

3.1 History of PCB contamination

The Danish chemist Søren Jensen (Figure 3.1) discovered the environmental PCB contamination during his work as analytical chemist at Stockholm University. In 1964 he started on a project estimating the levels of DDT and other organochlorine pesticides and metabolites in human fat and wildlife in Sweden. For the determination of the pollutants he used a gas chromatograph with electron-capture detector, a rather new method, and his instrument was also very simple compared to routine instruments nowadays (Figure 3.2):

[27] Hansen E, Grove A. PCB/PCT-forurening. En udredning om forbrug, forurening og transportveje for PCB og PCT i Danmark. Miljøstyrelsen, 1983.
[28] Miljøministeriets bekendtgørelse nr. 718 af 9. oktober 1986 om begrænsninger i anvendelsen af PCB og PCT
[29] Miljøministeriets bekendtgørelse nr. 925 af 13. december 1998 om PCB, PCT og erstatningsstoffer herfor.
[30] Maag J, Lassen C. PCB i apparater i Danmark. Arbejdsrapport fra Miljøstyrelsen nr. 15, 2000.
[31] Brevik K, Sweetman A, Pacyna, JM, Jones, KC. Towards a global historical emission inventory for selected PCB congeners — A mass balance approach 3. An update. Science Total Environment 2007; 377: 296–307.

Fig. 3.1: Søren Jensen (Stockholm University).

Figure 3.2: The old gas chromatograph Søren Jensen used for the discovery (own photo).

Based on the gas chromatogram of a purified extract of human fat samples he saw up to 14 unknown peaks in addition to DDT and its metabolites. He analyzed eagle feathers from the zoological specimen bank dating back to 1888 and found that the unknown substances first began to appear in samples from 1942, before the introduction of DDT (in 1945). Thus, it could not be metabolites of DDT or other chlorinated pesticides. In collaboration with ecologists he analyzed further samples of pike and salmon and found a similar pattern of unknown peaks, but, in an elk fat sample, there were only chlorinated pesticides. Hence, it seemed that the problem was concentrated to the aquatic environment. Treatment of the extracts with concentrated sulfuric acid or sodium hydroxide destroyed DDT but not the unknown peaks which indicated that the unknown substances could only contain carbon, hydrogen and halogens. A sample taken from a very contaminated white-tailed eagle from the Stockholm archipelago was analyzed by mass spectrometry, a new technique at that time; it was found that the parent hydrocarbon was biphenyl, and that it further only contained chlorine. As he did not know the uses of PCB, he asked around, and obtained a sample from Bayer, a German company who produced the technical product Clophen A50. When he analyzed that sample he noted the peaks with similar retention time as the unknown in the wildlife samples. After two years of research PCB was fully identified and quantified, and the result was published in a short communication.[32]

Some years later, Søren Jensen published a paper with the history of the discovery, where he also reports some data on human blood levels.[33] In Sweden 4 blood samples ranged from 6.9-14 ng PCB/g fresh weight, and 6 Japanese samples ranged 4.9-35 ng PCB/g fresh weight. The highest levels were in patients of Yusho (see later). Based on his discoveries, in 1972 Sweden was the first country to regulate open usage of PCB.

3.2 Persistent organic pollutant

After Søren Jensen's discovery scientists in other parts of the world increasingly began to analyze PCB in the environment. Now such monitoring is routinely being done worldwide. PCB has also been responsible for many out breaks of reproductive disease in natural populations of aquatic mammals, fish and fish-eating birds, especially in North America.[34]

[32] Jensen S. Report of a New Chemical Hazard. New Scientist 1966;32: 612
[33] Jensen S. The PCB Story. Ambio 1972;1:123-131.
[34] Gilbertson M. Effects on fish and wildlife populations. In: Kimbrough and Jensen (eds). Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.

PCB was among the initial 12 substances and substance groups included in the Stockholm Convention on Persistent Organic Pollutants (POPs) which was decided in Stockholm in May 2001, and which entered into force in 2004.[35] The criteria for being a persistent organic pollutant are shown in Table 3.1:

Table 3.1: Criteria for persistent organic pollutants in the Stockholm Convention (www.pops.int).

Persistence	Half-life in	Water > 2 months
		Soil > 6 months
		Sediment > 6 months
	Other evidence	
Bioaccumulation	Bioconcentration/bioaccumulation factor in aquatic species > 5000	
	Log Kow > 5	
	Other evidence such as high bioaccumulation in other species	
	Monitoring data in biota indicating bioaccumulation potential	
Potential for long-range environmental transport	Measured levels in locations distant from the release that are of potential concern	
	Monitoring data showing long-range environmental transport via air, water or migratory species	
	Environmental fate properties and/or model results that demonstrate a potential for long-range transport	
	For a chemical that migrates through the air its half-live in air > 2 days	
Adverse effects	Evidence of adverse effects to human health or to the environment	
	Toxicity or ecotoxicity data that indicate a potential for damage to human health or to the environment	

In 2009 the Stockholm Convention established a PCB Elimination Network (PEN) for information exchange and training, especially the third world, where PEN assists with elimination of out-phased PCB equipment and PCB waste.

3.3. Measurements of PCB in ambient air

Total PCB and PCB congeners are seldom monitored in ambient air, because their levels are mostly considered insignificant, and concentrations are very much dependent of meteorological conditions (air temperature, humidity, wind). In an early German study by Wittlinger and Ballschmiter (1987) the measured levels in urban areas were 0.35-2.60 ng PCB/m^3 and in rural areas only 0.12 -0.23 ng PCB/m^3. The average was 0.8 ng PCB/m^3.[36] In that study quantification of PCB was based on 5 congeners (PCB28, PCB52, PCB118, PCB138, and PCB180). In rural area most (80%) of the PCB congeners with 3-7 chlorine atoms and a vapor pressure > 10^{-4} Pa occur as vapor. In urban area more of the PCB will be adsorbed to particles than in rural areas; for instance 50% will be absorbed for congeners with seven chlorine atoms. PCB congeners with 1-3 chlorine atoms are expected to be >95% in the gas phase.[37]

The PCB levels in the air monitored from 1996-2002 in Chicago were strongly influenced by temperature and concentrations ranged 0.1-0.3 ng/m^3 in the winter, and up to 5-16 ng/m^3 were measured on hot

[35] www.pops.int
[36] Wittlinger R, Ballschmiter K. Global baseline pollution studies XI. Chemosphere 1987; 16: 2497-2513.
[37] Wittlinger R, Ballschmiter K. Isomer-specific analysis of polychlorobiphenyls (PCB) in air. Fresenius Z Anal Chem 1987; 327: 51-52.

summer days. The major congeners were a dozen of low-chlorinated congeners, and hexachlorinated and higher biphenyls were almost absent.[38]

A US study showed that in neighborhoods with industrial facilities, which produced electrical PCB capacitors during the years 1945 to 1977, the towns were contaminated by PCB. The measured ΣPCB sum of the 12 congeners: PCB28, PCB74, PCB99, PCB105, PCB118, PCB153, PCB170, PCB180, PCB183, PCB187 and PCB194 (*but without correction factor!)* in ambient air ranged from 0.1 - 4.0 ng/m^3 (median: 0.7 ng/m^3).[39] These were approximately twice the levels (0.08-2.37 ng/m^3; median: 0.43 ng/m^3) measured in a similar town up the river which were not directly polluted from the point source.

The ambient air concentrations of dioxin-like PCBs are even lower and may be difficult to quantify. The background concentration of the sum of coplanar PCBs in ambient air was 3-5 pg/m^3 in the Netherlands, and the concentration of specifically PCB126 was 0.3 pg/m^3, and that corresponded to 77% of total dioxin-equivalents (TEQs) in the samples.[40]

A study in Birmingham in the UK showed that the most important source of PCB pollution of ambient air originated from indoor air.[41] The indoor PCB levels (mean: 9 ng/m^3) were 30 fold higher than outdoor levels (mean: 0.3 ng/m^3) in the UK. Quantification was made as the sum of 27 PCB peaks without correction factor used to get the total PCB.[42]

4. PCB in buildings

A large recent survey by Grontmij/COWI estimated that a large part of the Danish buildings from the period, when PCB was used, still contain materials contaminated with PCB.[43] A summary of the findings is shown in Table 4.1:

[38] Ludewig G, Lehmann L, Esch H, Robertson LW. Metabolic activation of PCBs to carcinogens in vivo - a review. Environ Toxicol Pharmacol 2008; 25: 241-246.
[39] Fitzgerald EF, Shrestha S, Palmer PM, Wilson LR, Belanger EE, Gomez MI, Gayo MR, Hwang S. Polychlorinated biphenyls (PCBs) in indoor air and in serum among older residents of upper Hudson River communities. Chemosphere 2011; 85: 225-231.
[40] Lopez Carcia A, den Boer AC, de Jong APJM. Determination of non- and mono-*ortho*-polychlorinated biphenyls in background ambient air. Environ Sci Technol 1996; 30: 1032-1037.
[41] Jamshidi A, Hunter S, Hazrati S, Harrad S. Concentration and chiral signatures of polychlorinated biphenyls in outdoor and indoor air and soil in a major U.K. conurbation. Environ Sci Technol 2007; 41: 2153-2158.
[42] Currado GM, Harrad S. Comparison of polychlorinated biphenyl concentrations in indoor and outdoor air and the potential significance of inhalation as a human exposure pathway. Environ Sci Technol 1998; 32: 3043-3047.
[43] Langeland M, Jensen MK. Kortlægning af pcb i materialer og indeluft. Fase 2 rapport. Grontmij/COWI, april 2013.

Table 4.1 Estimation of PCB in Danish buildings (Langeland and Jensen 2013).

Building type	**Number of buildings with PCB-containing materials above three concentrations limits and the share (%) of the total building mass (90% confidence interval)**		
	≥ 0.1 mg/kg	≥ 50 mg/kg	≥ 5 000 mg/kg
One- and two family houses	390 000-470 000 67-79 %	80 000-140 000 13-24 %	20 000-60 000 4-11 %
Apartment blocks	12 600-14 100 84-95 %	3 600-5 900 24-40 %	1 000-2 700 7-18 %
Private office building	13 000-18 600 60-86 %	4 900-11 000 23-51 %	1 600-6 000 8-30 %
Public institutions and offices	In sealing: 4 700-5 700 22-27 % In paint an floor materials: 13 000-18 000 62-83 %	In sealing: 2 100-2 900 10-13 % In paint an floor materials: 2 400-6 500 11-30 %	In sealing: 1 200-1 800 6-9 % In paint an floor materials: 300-2 800 1-13 %

In 2007-2008 in Toronto, Canada, a PCB measurement campaign and a GIS-based stock estimation was undertaken. It showed that 95 buildings or 14% had detectable quantities of PCBs (83 congeners) present in sealants, with concentrations from 0.57 g/kg (0.057%) to 82 g/kg (8.2%).[44] The amount of remaining PCB-containing sealants in the city of Toronto was estimated to 13 tons. Mass balance calculations showed that up to 9% had been lost via volatilization alone.

The primary sources of PCB in indoor air are evaporation of PCB from sealing, paint, fluorescent lighting and other products containing PCB. Airborne PCB is partly adsorbed to airborne dust which may deposit itself on surfaces like walls, floors, and furniture/equipment. Temperature changes may also cause condensation and/ evaporation of PCB such surfaces. PCB in the primary source may also migrate into neighboring materials inside the walls.

4.1 Historical use in buildings

From the 1950s and to mid-1970s PCB was extensively used in building materials and in buildings during that time. PCB products were more expensive but had preferable properties (stability etc.) for the purpose. These PCB products are still present in the buildings and can be released and pollute the indoor climate and expose the dwellers. Examples of Building materials with PCB: [45]

- Elastic (rubber) sealants and caulking agents between elements and around windows and doors, often polysulfide's (e. g. Thiokol®)
- Sealing's of thermo windows
- Fire retarding paints for roof materials and noise insulation
- Weather resistant paint for outdoor surfaces
- Paints for industry and cellar floors (e.g. Acrydur®)
- Special cement mixtures

[44] Robson M, Melymuk L, Csiszar S, Giang A, Diamond M, Helm P. Continuing sources of PCBs: The significance of building sealants. Environ Int 2010; 36: 506-513.

[45] Jensen AA, Schleicher O, Sebastian W, Trap N, Zeuthen F. Forekomst af PCB i en- og tofamiliehuse. Report til Erhvervs- og Byggestyrelsen, december 2009. http://www.ebst.dk/file/74259/pcb_enogtofamiliehuse.pdf, http://www.mst.dk/NR/rdonlyres/B281D13B-D668-43C2-8EBE-83F97105E83B/0/pcb_enogtofamiliehuse.pdf

- Floor lacquers and fillers
- Plasticizers in cables and floors of PVC,
- Oils in ballasts for fluorescent lighting.

The concentration varied from few milligram/kg (ppm) to around 30 % in solid materials such as sealing and caulking agents and to around 60% in capacitor oils.

It seems that fluorescent lightings with PCB containing ballasts are still not completely phased out of use many places. For instance, in December 2013 the US Environmental Protection Agency has updated its guidance to schools on PCB-containing lighting fixtures.[46]

4.2 PCB levels in sealing and paints

PCB usages in elastic sealing and paints for indoor- or outdoor uses are the best known and are estimated to be the primary sources of PCB in the indoor climate in Denmark. The extents to which fluorescent lightings with PCB ballasts are still in use in Denmark are presently unknown. Thermo windows with PCB still in use will probably mainly be a waste problem. In a Danish study of wastes from demolition of buildings constructed in the PCB period, most samples of thermo window glue and putty contained more than 50 mg PCB/kg, which is the official limit for PCB waste.[47] In this study the highest concentrations of PCB were in outdoor window sealing and in outdoor wall paint. For secondary contaminated concrete and bricks PCB levels were over 50 mg/kg.

In the first Swedish studies from the 1990s the PCB concentrations determined in sealing materials inside and outside of buildings in use ranged between 9 and 19 weight %.[48]

In the recent study of PCB in indoor air in the apartments in Farum Midtpunkt 20 samples of elastic sealing were also analyzed for 24 PCB congeners.[49] Only one out of the 24 congeners was not quantifiable. Most abundant congeners were PCB 52, PCB66, PCB74, PCB101, PCB118, PCB138 and PCB153. The main results are shown in Table 4.2:

Table 4.2: PCB (mg/kg) in 20 samples of elastic sealants from Farum Midtpunkt (Frederiksen *et al.* 2012).

	Mean	Median	Max	Max in %
ΣPCB_{24}	100817	10140	221677	22
ΣPCB_{6}	50430	33042	143686	14
PCB_{total}	252150	165208	718430	71

In 18 case studies of apartments and institutions in Denmark the average PCB concentration in elastic sealing was determined to be 100 000 mg PCB_7x5/kg.[50] In one case - a child care home - a sealing sample contained 240 000 mg PCB_7x5/kg. The results are shown in Figure 4.1:

[46] http://www.epa.gov/epawaste/hazard/tsd/pcbs/pubs/ballasts.htm; http://yosemite.epa.gov/opa/admpress.nsf/d0cf6618525a9efb85257359003fb69d/2e548f3ed779c8a085257c3f006147ad!OpenDocument

[47] Alslev BP, Kampmann K, Gjødvad JF. Rapport over data fra gennemførte renoveringer og nedrivninger af bygninger opført i perioden 1950-1977 med PCB. Miljøprojekt nr. 1465. København: Miljøstyrelsen, 2013. http://www2.mst.dk/Udgiv/publikationer/2013/01/978-87-92903-87-7.pdf

[48] Jansson B, Sandberg J, Johansson N, Åstebro A: PCB i fogmassor - stort eller litet problem? Rapport 4697. Solna: Naturvårdsverket, 1997.

[49] Frederiksen M, Meyer HW, Ebbehøj NE, Gunnarsen L. Polychlorinated biphenyls (PCBs) in indoor air originating from sealants in contaminated and uncontaminated apartments within the same housing estate. Chemosphere 2012; 89: 473-479.

[50] Haven R, Langeland M. Afhjælpningstiltag ved forhøjede PCB-niveauer i indeklimaet. Erhvervs- og Byggestyrelsen og Socialministeriet, marts 2011. http://pcb-guiden.dk/file/159799/pcb_afhjaelpningstiltag.pdf

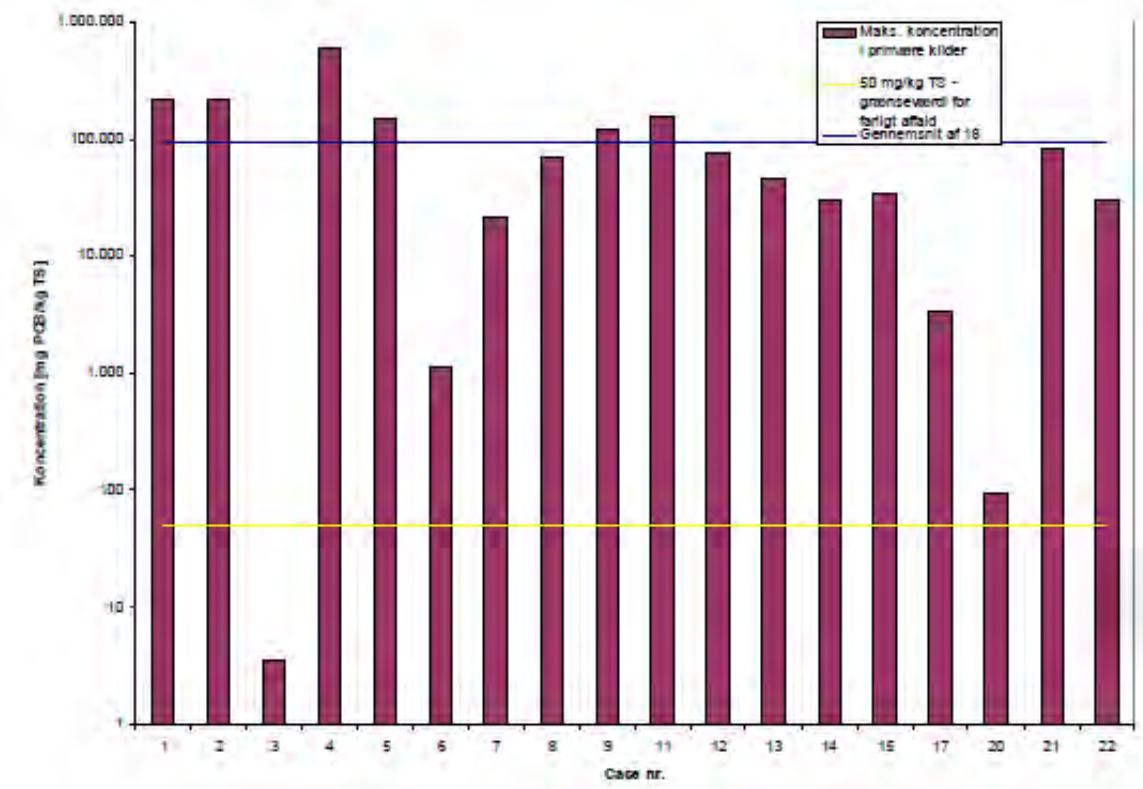


Figure 4.1: Concentration mg/kg dry weight of PCB in primary sources (elastic sealing) in 18 cases from Denmark (Haven and Langeland 2011).

4.3 Entry and spreading of PCB from elastic sealing's into nearby materials

Studies in Sweden about ten years ago have shown that PCB in sealants to some extent will migrate and spread to adjoining materials depending on the properties of the materials. In one study the building materials investigated were concrete, brick, wood, light concrete, plaster/light concrete in combination, marble and polyurethane foam.[51] All materials had high levels of PCB in the layers adjacent to the PCB-sealant, probably due to a physically penetration of the sealant and PCB into the material depending on its porosity. In the study large amount of PCB was removed by grinding 2-6 mm of the layers of materials adjacent to an elastic sealant, and the collected grinding dusts were analyzed for PCB_7. The medians of the PCB concentration in dust obtained at the three grinding depths are shown in Table 4.3:

Table 4.3: Migration of PCB into adjacent building materials (Sundahl *et al.* 2001).

Adjacent material	Median PCB concentrations for various grinding depths in adjacent material as % of the content in the sealing		
	0-2 mm	2-4 mm	4-6 mm
Concrete	14%	4%	3%
Brick	14%	6%	2%
Wood	2.5%	0.2%	0.07%
Light concrete*	7.5%	4.5%	1.8%
Plaster/light concrete*	27.5%	9.9%	0.5%

*average

[51] Sundahl M, Hjorthage A, Torstensson, Ek-Olausson B. Spread of PCB from PCB-containing elastic sealant to adjacent building materials Borås: SP Swedish National Testing and Research Institute, Report 2001:2, 2001. (*in Swedish*).

Based on these findings it was recommended to grind at least 2-3 mm of the adjacent material in connection with PCB renovation.

The investigations of Farum Midtpunkt showed that about 500 kg PCB had been used in the group of buildings.[52] Most PCB (82%) was still contained in the elastic sealing but parts had migrated to adjacent materials, and a PCB-contamination of 50 ppm (mg/kg) - corresponding to the limit for hazardous waste - was found to have penetrated almost 30 mm into concrete, 10 mm into wood and 70 mm into Masonite. In a recent Danish report most published studies about migration of PCB from sealants are reviewed.[53]

4.4 Replacement of PCB containing sealants

Determination of a level of >500 mg PCB_7/kg in a sealant is the recommended value for PCB renovation of buildings in Sweden by removal of a PCB sealant, and substitution with new sealant without PCB should improve the situation.[54]

The Swedish study investigated the data mentioned above.[55] After 12 – 16 months a sample of the new sealant was analyzed, and although it was contaminated with PCB migrated from surrounding proximate contaminated materials, the levels were lower than 30 mg PCB_7/kg (30 ppm).

A PCB renovation in 1999 of a seven stories apartment house in Stockholm has been studied.[56] About 600 meter of visible external PCB-contaminated elastic sealing was removed by knife. Residual sealant and 2 mm concrete around were removed with a grinder, and the dust collected by a vacuum cleaner. The facade was also cleaned by high-pressured water. The mass balance showed that 70 kg PCB was removed in addition to the sealant, 2-20 gram PCB was removed through waste water, 2.5 gram PCB to the soil and 0.6-1.3 gram PCB was released to the air.

In Sweden and Denmark several guidelines and instructions have been published on how to renovate PCB contaminated buildings, both to protect the workforce during this activity and to manage the waste safely.[57,58,59,60]

An alternative way to reduce the indoor PCB pollution may be to encapsulate the primary PCB source (sealing) by covering it up e.g. aluminum foil. In a Danish study this method has had limited success with only a small reduction in the PCB indoor air levels.[61] However, removal of primary and secondary sources,

[52] Haven R, Langeland M. Afhjælpningstiltag ved forhøjede PCB-niveauer i indeklimaet. Erhvervs- og Byggestyrelsen og Socialministeriet, marts 2011. http://pcb-guiden.dk/file/159799/pcb_afhjaelpningstiltag.pdf
[53] Andersen HV, Gundersen L, Kampmann K. Kortlægning af eksisterende viden om indtrængning af PCB fra fuger til beton. Miljøprojekt nr. 1464. Miljøstyrelsen, 2013. http://www2.mst.dk/Udgiv/publikationer/2013/01/978-87-92903-86-0.pdf
[54] www.sanerapcb.nu
[55] Sundahl M, Hjorthage A, Torstensson, Ek-Olausson B. Spread of PCB from PCB-containing elastic sealant to adjacent building materials Borås: SP Swedish National Testing and Research Institute, Report 2001:2, 2001. (*in Swedish*).
[56] Åstebro A, Jansson B, Bergström U. Emissions during replacement of PCB containing sealants – a case study. Organohalogen Compounds 2000; 46: 248-251.
[57] Branchevejledning om håndtering og fjernelse af PCB-holdige bygningsmaterialer. Branchearbejdsmiljørådet for bygge og anlæg, 2010.
[58] Golder Assoc. Vejledning og beskrivelse for udførelse af PCB-sanering. Dansk Asbestforening, 2010.
[59] Rex GB, Sikander E. Åtgärder vid sanering av PCB-haltiga fogmassor - Studie och rekommendationer om skyddsåtgärder, utrustning och rutiner. Rapport från Riv- och Saneringsentreprenörerna inom Sveriges Byggindustrier, Februari 2006. http://www.rivosaner.se/publikationer/filer/rapport_atgarder_vid_sanering_av_pcb-060228.pdf
[60] http://anvisninger.dk/Publikationer/Sider/Renovering-af-bygninger-med-PCB.aspx
[61] Haven R, Langeland M. Afhjælpningstiltag ved forhøjede PCB-niveauer i indeklimaet. Erhvervs- og Byggestyrelsen og Socialministeriet, marts 2011. http://pcb-guiden.dk/file/159799/pcb_afhjaelpningstiltag.pdf

heating, coverage and ventilation were efficient, and the result was low levels of PCB in the indoor air (Figure 4.2):

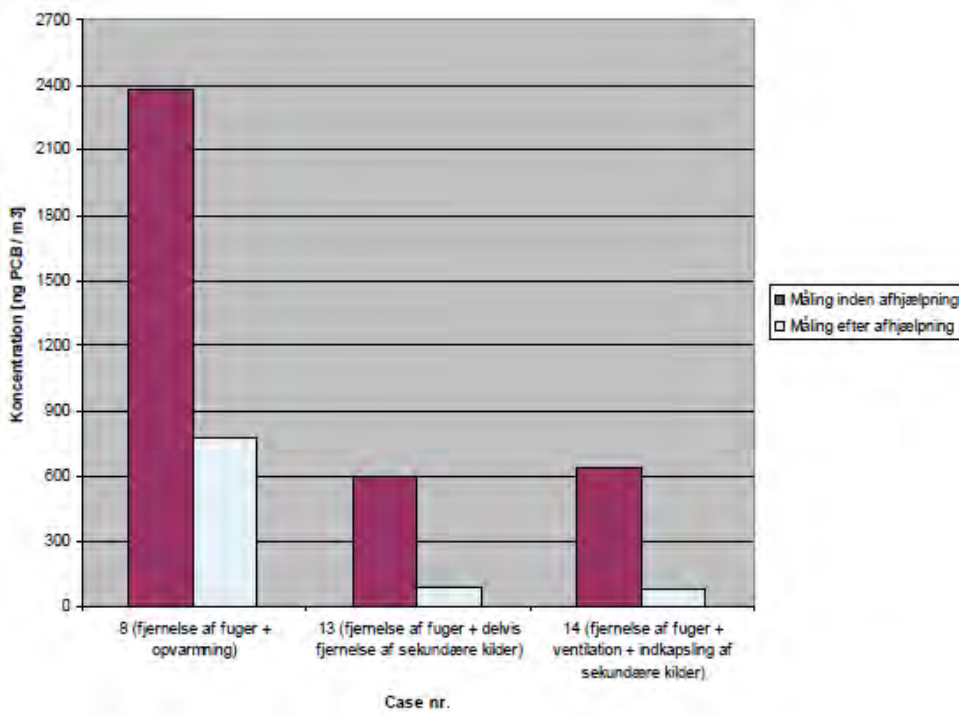


Figure 4.2: Effect of removal of primary PCB sources etc. (from Haven and Langeland 2011).

Removing primary sources, followed by using wall papers with active carbon to enclose secondary sources efficiently reduced PCB in indoor air 45 folds from 4500 ng/m^3 to 100 ng/m^3. However, this use was considered doubtful because of the potential fire risk from the wall paper.

USEPA has a website: "PCBs in Caulk in Older Buildings", with guidance to minimize PCB exposure in schools and other buildings. The first steps include improved ventilation and cleaning.[62]

Renovation of an elementary school in the USA with increasing filtered outdoor air ventilation, encapsulating caulk with polyethylene tape and silicone caulk, and constructing a physical barrier as a false wall with aluminum-backed fiberglass insulation board and a gypsum board over the encapsulated material were shown to be effective at reducing exposure concentrations of PCBs in indoor air of a school and also preventing direct contact with PCB caulk.[63] The caulk contained between 1830 and 29400 ppm PCB as Aroclor 1260. The average PCB level in the classroom air was 533 ng/m^3, before the renovation took place and 95 ng/m^3 after.

[62] http://epa.gov/pcbsincaulk/index.htm
[63] MacIntosh DL, Minegishi T, Fragala MA, Allen JG, Coghlan KM, Stewart JH, McCarthy JF. Mitigation of building-related polychlorinated biphenyls in indoor air of a school. Environmental Health 2012, 11:24. http://www.ehjournal.net/content/11/1/24

In a German study of a successful PCB renovation of a public office building in Kiel, where active coal wall-paper was used, the indoor air levels of PCB directly after the renovation averaged 95 ng/m^3 and some month's later even 45 ng/m^3.[64]

4.5 Evaporation of PCB congeners and temperature dependence

PCBs are not very volatile; however, both the mixtures and single congeners do have some vapor pressures, which in general decrease with increased chlorine content of the PCB, however, the chlorine substitution pattern has also influence. PCB in sealing and other materials will therefore release vapors until saturated air concentrations are reached. The saturated air concentrations will be maximum concentrations in indoor air to be reached in praxis. That means that the more volatile lower chlorinated congeners will reach higher concentrations than the less volatile higher chlorinated congeners, and these congeners will dominate in samples of indoor air. In Table 4.4 vapor pressures and calculated saturated air concentrations of some important chlorinated PCB congeners are shown.

Table 4.4: Vapor pressures (from Table 2.7) and calculated air saturation concentrations of PCB congeners

Congener	Molecular mass	Vapor pressure in Pa at 25°C and 1 atm.	Saturated air concentration in ng/m^3 at 25°C and 1 atm.
PCB 28	257.54	3.4 x 10^{-2}	3 400 000
PCB 52	291.99	1.6 x 10^{-2}	180 000
PCB 77	291.99	2.2 x 10^{-3}	240 000
PCB 101	326.43	3.4 x 10^{-3}	44 000
PCB 118	326.43	1.2 x 10^{-3}	14 000
PCB 138	360.88	5.1 x 10^{-4}	7300
PCB 153	360.88	6.8 x 10^{-4}	9500
PCB180	395.32	1.3 x 10^{-4}	1940

1 Atm. (1.013x10^5 Pa)

Since there is some degree of uncertainty regarding values of the vapor pressures, the calculated saturated air concentrations are approximates to explain the theoretical relative concentration of the congeners. The approximate average evaporation rates also illustrate the great difference among the PCB homologue groups (see Table 4.5): [65]

Table 4.5: Approximate evaporation rates of PCB homologue groups (Erickson 2001).

PCB congener group	Approx. evaporation rate at 25°C (g/m^{3}h)
Trichlorobiphenyls	1.7 x 10^{-2}
Tetrachlorobiphenyls	4.2 x 10^{-3}
Pentachlorobiphenyls	1.0 x 10^{-3}
Hexachlorobiphenyls	2.5 x 10^{-4}
Heptachlorobiphenyls	6.2 x 10^{-5}

[64] Mohr S, Heinzow B, Ostendorp G, Pitulle H. Erfahrungen mit einem PCB-Sanierungsfall – Das Mercator-Hochhaus in Kiel. VDI Wissenforum Schadstoffe in Innenräumen, Manheim, 2001.

[65] Erickson MD. PCB properties, uses, occurrence, and regulatory history. In PCBs: Recent Advances in Environmental Toxicology and Health Effects. Eds. Robertson LW, Hansen LG. University Press of Kentucky, 2001.

In an American school study the estimated emission rate from caulk was estimated to 53-3100 µg PCB/hour depending on the area of the caulk and the PCB concentration in it. Also from paint the emission rate was high.[66]

The vapor pressures of PCB congeners will increase with increasing temperature and more PCB can be in the vapor phase as seen in Figure 4.3: [67]

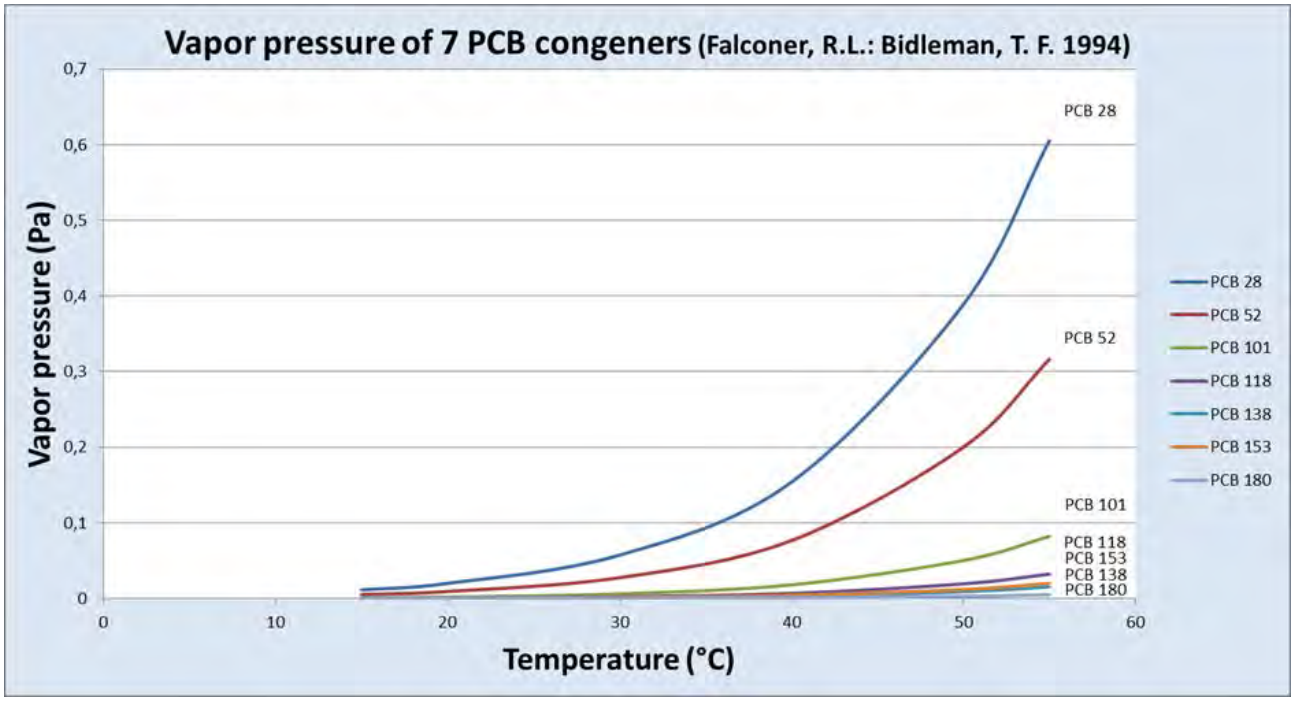


Figure 4.3: Temperature dependence of vapor pressure of PCBs (Nadja Lyng 2013).

The temperature in a room will therefore have great influence on the measured PCB levels in indoor air. The rapid increase with increasing temperature of PCB concentration in indoor air is illustrated by a study of PCB-contaminated flats in Farum Midtpunkt (Figure 4.4): [68]

[66] Thomas K, Xue J, Williams R, Jones P, Whitaker D. Polychlorinated Biphenyls (PCBs) in School Buildings: Sources, Environmental Levels, and Exposures. EPA/600/R-12/051. US EPA, September 2012.
[67] Nadja Lyng. PCB og ventilation. Præsentation Møde i PCB-netværket 16. april 2013. Sbi.dk/pcb; Falconer RL, Bidleman TF. Vapor pressures and predicted particle/gas distributions of polychlorinated biphenyl congeners as functions of temperature and ortho-chlorine substitution. Atmosph Environ 1994; 28: 547-554.
[68] Haven R, Langeland M. Afhjælpningstiltag ved forhøjede PCB-niveauer i indeklimaet. Erhvervs- og Byggestyrelsen og Socialministeriet, marts 2011. http://pcb-guiden.dk/file/159799/pcb_afhjaelpningstiltag.pdf

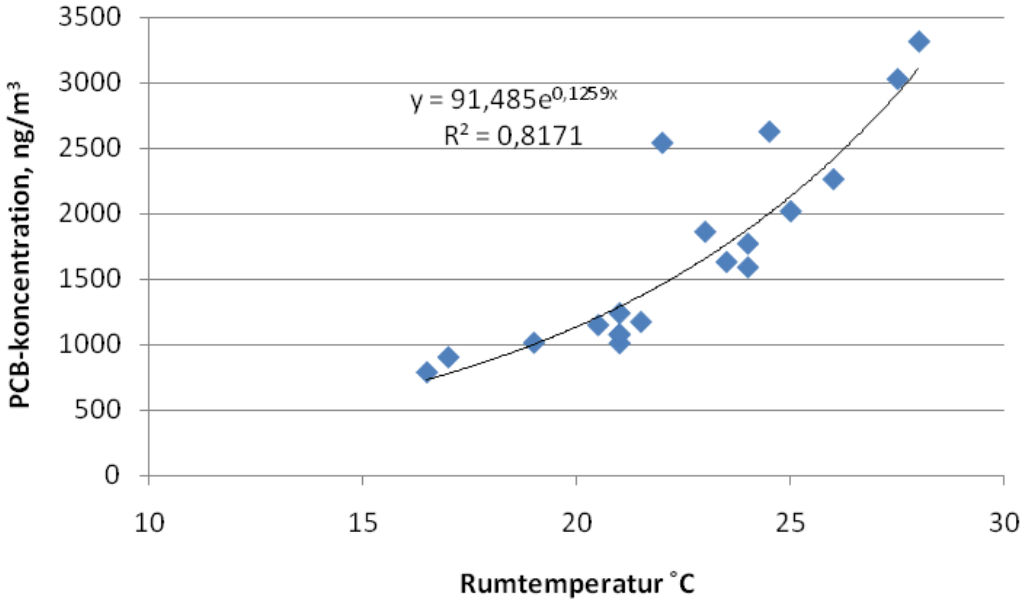


Figure 4.4: Temperature dependence of PCB in indoor air (Haven and Langeland 2011).

When the temperature increases the indoor air may contain more PCB, and when the temperature decreases, PCB will condense on dust or deposit on surfaces, including painted walls and furniture. When the temperature raises next time evaporation occurs from both the primary sources, contaminated building materials (secondary sources) and deposits on surfaces (tertiary sources).

This temperature dependence means that there will be higher PCB concentrations in indoor air measured in the summer, when temperature is high outside, compared with PCB concentrations in the winter. This is illustrated with the significantly higher summer levels in Figure 4.5:[69]

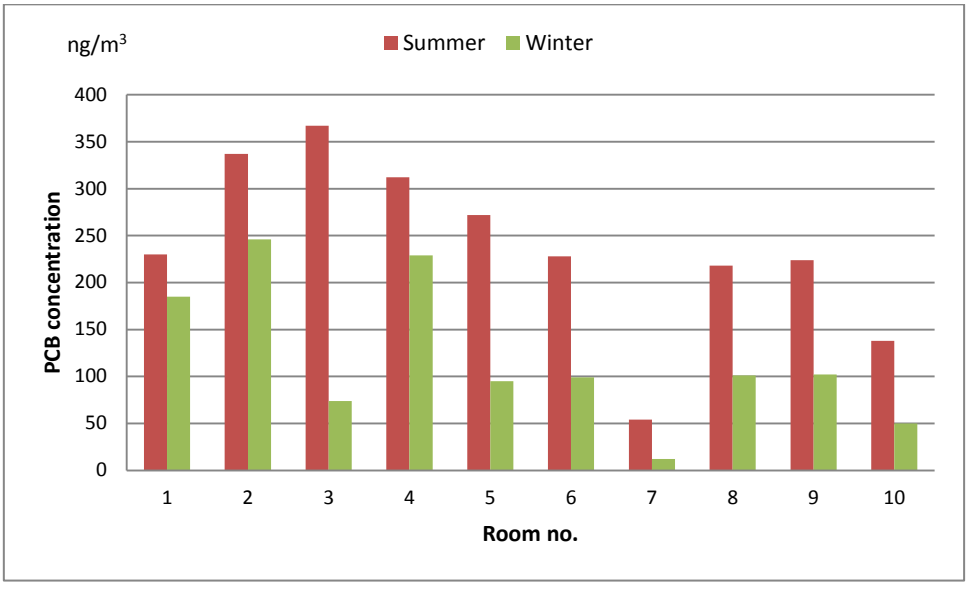


Figure 4.5: PCB in indoor air in the same room in summer and winter (based on data from Balfanz et al. 1993).

[69] Balfanz E, Fuchs J, Kieper H. Sampling and analysis of polychlorinated biphenyls (PCB) in indoor air due to permanently elastic sealants. Chemosphere 1993; 26: 871-880.

4.5 Measurements of PCB in indoor air in buildings

In the case of indoor air measurements of PCB, the careful planning of sampling and the entire measurement strategy are of particular significance, since an inappropriate measurement strategy may contribute to more overall uncertainty of the result than the measurement procedure itself. A measurement guidance specific for Denmark has been developed.[70]

Sampling place in the building has to be decided after an evaluation of the potential PCB sources in the room, and sample size and sampling period have to be decided in accordance with the aim of the study and the analytical limit of detection obtained by the method. For indoor PCB measurements of PCB_7 a detection limit of 1 ng/m^3 will be sufficient and easy to obtain but for coplanar, dioxin-like PCB the analytical method have to be more sensitive.

Some of the earlier screening studies in Sweden were with passive sampling equipment revealing relative results. For instance, it was useful to show that the levels of PCB in air of PCB contaminated flats were about 60 folds higher than in the air in uncontaminated flats.[71]

In order to get quantitative results an active sampling method has to be used, where air is drawn through a particle filter for detaining particle-borne PCB followed by a tube containing an adsorption material, such as polyurethane foam (PUF), for the PCB-vapor. Most PCB in indoor air will typically be in the vapor phase. In a German study 89 % of the PCB was found in the PUF tube and only 11 % in the filter (Balfanz et al. 1993). In a Danish study where the total PCB concentration was 2100 ng/m^3 the particle part was only 125 ng/m^3 or <6 %.[72]

In 2010 the Danish Building authorities published guidelines for measurement of PCB in indoor air based on German VDI 4300 Blatt 2 (1997) and the international standard EN/ISO 16000-12:2008, which specifies the planning of measurements for polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs) polychlorinated dibenzofurans (PCDFs) and polycyclic aromatic hydrocarbons (PAHs) in indoor air.[73] The specific analytical methods for measurement of the classical PCBs and the co-planar PCB are described separately in other standards.[74,75,76,77]

In 2013 the Danish Building Research Institute (SBi) at Aalborg University has published a practical Internet guide (*in Danish*) about how to investigate and assess PCB in buildings.[78]

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[70] Vejledning for måling af PCB i indeklimaet. Erhvervs- og Byggestyrelsen, november 2010. Based on: Jensen AA, Fuglsang K, Schleicher O. Notat om målemetode for indeklimamåling af PCB. Force Technology, December 2009. http://www.ebst.dk/file/132121/pcb_maalemetode.pdf

[71] Johansson N, Hanberg A, Bergek S, Tysklind M. PCB in sealant is influencing the levels in indoor air. Organohalogen Compounds 2001; 52: 436-440.

[72] Haven R, Langeland M. Afhjælpningstiltag ved forhøjede PCB-niveauer i indeklimaet. Erhvervs- og Byggestyrelsen og Socialministeriet, maj 2011. http://pcb-guiden.dk/file/159799/pcb_afhjaelpningstiltag.pdf

[73] Vejledning for måling af PCB i indeklimaet. Erhvervs- og Byggestyrelsen, november 2010. Based on: Jensen AA, Fuglsang K, Schleicher O. Notat om målemetode for indeklimamåling af PCB. Force Technology, December 2009. http://www.ebst.dk/file/132121/pcb_maalemetode.pdf

[74] VDI 2464 Blatt 1. 2009-09. Messen von Immissionen - Messen von Innenraumluft - Messen von polychlorierten Biphenylen (PCB) - GC/MS-Verfahren für PCB 28, 52, 101,138, 153, 180.

[75] VDI 2464 Blatt 2. 2009-09. Messen von Immissionen - Messen von Innenraumluft - Messen von polychlorierten Biphenylen (PCB) - HR-GC/HR-MS-Verfahren für coplanare PCB.

[76] ISO 16000-13: 2008. Determination of total (gas and particle-phase) polychlorinated dioxin-like biphenyl (PCBs) and polychlorinated dibenzo-p-dioxins/dibenzofurans (PCDDs/PCDFs) – Collection on solid sorbent-backed filters.

[77] ISO 16000-14: 2009. Indoor air – Determination of total (gas and particle phase) polychlorinated dioxin-like biphenyls (PCBs) and polychlorinated dibenzo-p-dioxins/dibenzofurans (PCDDs/PCDFs) – extraction, clean-up and analysis by high-resolution gas chromatography and mass spectrometry.

[78] http://anvisninger.dk/Publikationer/Sider/Undersoegelse-og-vurdering-af-pcb-i-bygninger.aspx/Indhold

4.6 Typical indoor air levels of PCB

In general, background levels of PCB in indoor air are much higher than in outdoor air, where background atmospheric concentrations of PCB are 0.1-10 ng/m^3.[79] Levels of PCB in indoor air in buildings with PCB sources are less than 30 ng PCB/m^3. In buildings with remaining PCB sources PCB levels in indoor air are typically 50-100 folds higher. In indoor air the major PCB peaks are the lighter and more volatile PCBs, because these more volatile congeners evaporate at a higher degree than from the material sources in the building.

In the US up to 0.3 µg PCB/m^3 has been measured in public office buildings or 5-300 folds more than measured outside, and extremely high concentrations of 80-280 µg PCB/m^3 were measured in offices in a governmental building in Binghamton, New York, USA, after a famous transformer fire occurring in 1981.[80]

Recent examples of levels of PCB in indoor air in schools and other institutions showed levels up to 2700 ng/m^3 in Denmark and up to 39 000 ng/m^3 in Germany.[81]

The large building complex "Farum Midtpunkt" with approximately 300 PCB contaminated apartments out of 1645 was built in 1970-1974 in a suburb of Copenhagen. An investigation in 2011 measured 24 PCB congeners in indoor air samples. The results for ΣPCB_{24}, ΣPCB_6 and PCB_{total} are shown in Table 4.6: [82]

Table 4.6: PCB in indoor air (ng/m^3) of Farum Midtpunkt (Data from Frederiksen *et al.* 2012).

PCB in indoor air ng/m^3	Un-contaminated apartments			Contaminated apartments		
	Mean	Median	Max	Mean	Median	Max
ΣPCB_{24}	4.80	0.11	64.5	285	236	1060
ΣPCB_6	3.56	nd	50.7	206	172	769
$PCB_{total} = \Sigma PCB_6 \times 5$	17.8	nd	254	1030	859	3843

nd = <0.07-1.5 ng/m^3

Half of control apartments had PCB levels below the quantification limit of <0.07-1.5 ng/m^3 but every apartment with PCB from sealants had contaminated air samples. Only 7 of the analyzed 24 congeners were quantifiable in the samples from uncontaminated apartments, while a mean could be calculated for 15 congeners in contaminated apartments. The concentrations of the most abundant PCB-congeners measured in indoor air of the two types of apartments are illustrated in Figure 4.6:

[79] McLeod KE. Sources of emissions of polychlorinated biphenyls into the ambient atmosphere and indoor air. EPA-600/4-79-022, Research Triangle Park, 1979.
[80] Toxicological profile for polychlorinated biphenyls. Atlanta: ATSDR, November 2000.
[81] Jensen AA, Schleicher O, Sebastian W, Trap N, Zeuthen F. Forekomst af PCB i en- og tofamiliehuse. Report til Erhvervs- og Byggestyrelsen. København, december 2009. http://www.ebst.dk/file/74259/pcb_enogtofamiliehuse.pdf; http://www.mst.dk/NR/rdonlyres/B281D13B-D668-43C2-8EBE-83F97105E83B/0/pcb_enogtofamiliehuse.pdf
[82] Frederiksen M, Meyer HW, Ebbehøj NE, Gunnarsen L. Polychlorinated biphenyls (PCBs) in indoor air originating from sealants in contaminated and uncontaminated apartments within the same housing estate. Chemosphere 2012; 89: 473-479.

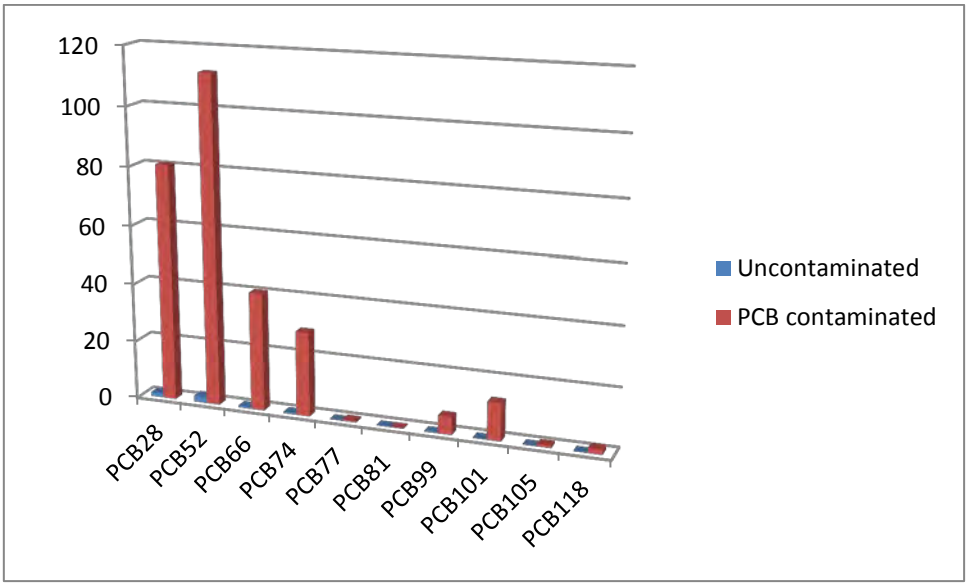

Figure 4.6: The most abundant PCB congeners in indoor air (ng/m^3) in apartments from Farum Midtpunkt (Based on data from Frederiksen et al. 2012).

Calculated as PCB_7 levels were almost the same, because PCB-118 could only be quantified in contaminated apartments and with a mean of 1.75 ng/m^3. The mean concentration of the dioxin-like PCBs was 3.2 ng/m^3 (has to be calculated as TEQs). There was a significant correlation between levels of PCB28 in sealant and in indoor air (see Figure 4.7): [83]

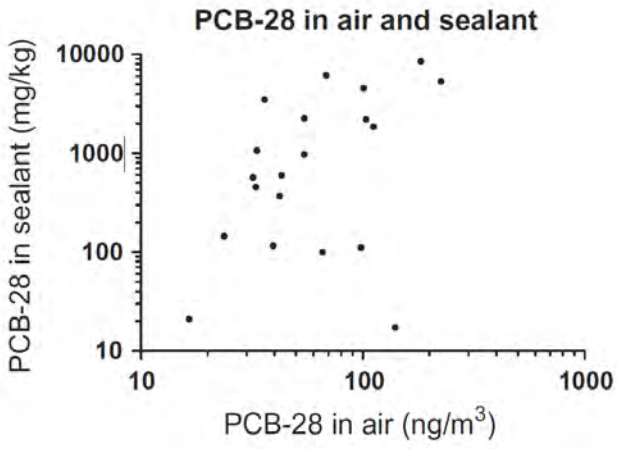

Figure 4.7: Correlation between PCB28 in sealants and indoor air (Frederiksen et al. 2012).

In a study of six schools in the United States of America (New York) contaminated with PCB mainly from caulk and paint the median PCB indoor air concentration was 318 ng/m^3 with a maximum concentration of 2920 ng/m^3, and the median PCB in dust was 22 ppm with a maximum of 87 ppm.[84] The PCB was determined as Aroclor 1254 having a similar PCB peak pattern as PCB in caulk. The relative concentrations of the single congeners were estimated to PCB110 > PCB101 > PCB95 > PCB52 > PCB70 >PCB118.

[83] Frederiksen M, Meyer HW, Ebbehøj NE, Gunnarsen L. Polychlorinated biphenyls (PCBs) in indoor air originating from sealants in contaminated and uncontaminated apartments within the same housing estate. Chemosphere 2012; 89: 473-479.
[84] Thomas K, Xue J, Williams R, Jones P, Whitaker D. Polychlorinated Biphenyls (PCBs) in School Buildings: Sources, Environmental Levels, and Exposures. EPA/600/R-12/051. US EPA, September 2012.

The commercial PCB mixtures used to make the various materials may also be different. PCB mixtures used in Germany in elastic rubber sealants were typically chlorinated mixtures with <50% chlorine, while PCB mixtures used e.g. in flame-retarded paints for roof plates were more highly chlorinated mixtures. These sources will therefore result in different congeners in the indoor air and dust. This is illustrated in Figure 4.8 showing different PCB patterns in indoor air, when the sources are respectively elastic sealants and flame retarded roof plates that were previously highly used in Germany.[85]

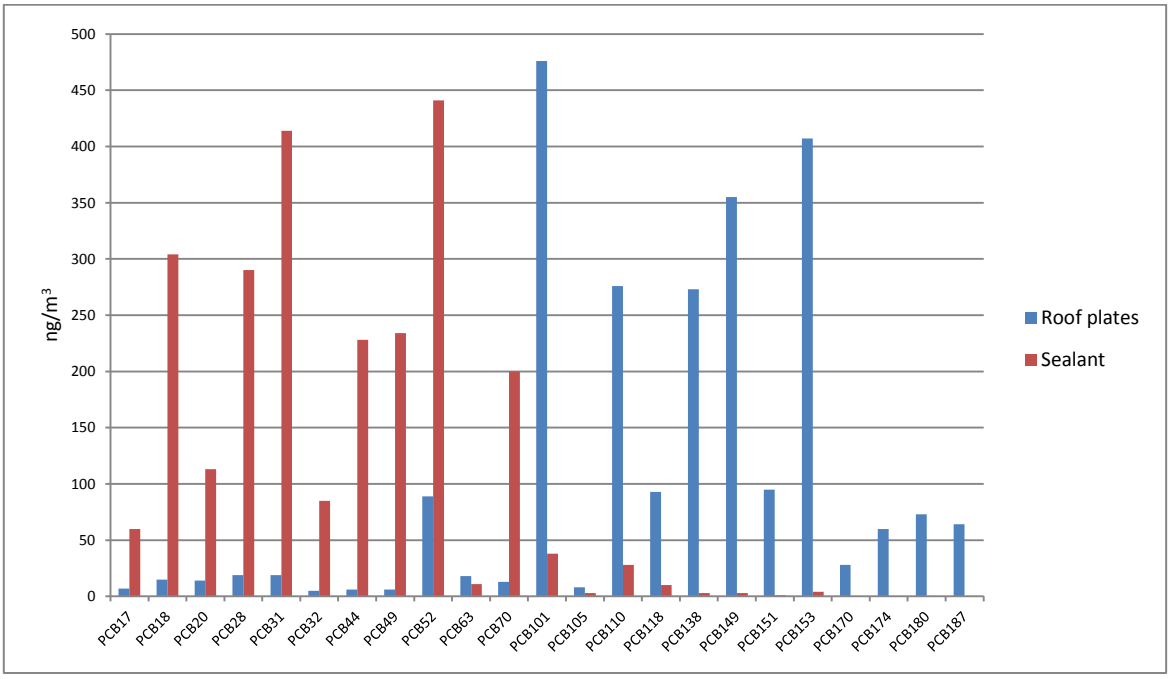

Figure 4.8: Example of two different PCB patterns in indoor air caused by different sources (Based on data from Kieper and Hemminghaus 2005).

The inhalation of vapors from an Aroclor 1242 mixture was studied in rats. The most prevalent PCB congeners measured in the air were PCB1, PCB4 and PCB8. The study revealed that mono-, di- and trichlorobiphenyls represented 90% of all vapor phase PCBs, while PCB 28 and PCB 52 accounted only for less than 5% and approx. 2% of all PCBs, respectively.[86]

These studies underline that PCB_6 and PCB_7 may not be so relevant for quantitation of PCB in indoor air originating from sealants, since only PCB28 and PCB52 of these are abundant, and many important low chlorinated congeners are not at all quantified with the applied methods.

Also another German study found the same different patterns regards PCB used in sealant and as flame retardant, and in addition that the flame retardant mixtures also produced more dioxin-like PCBs in the indoor air.[87] Dioxin-like PCB concentrations in the indoor air were between 0.3 and 5 pg TEQ_{PCB}/m^3. The

[85] Kieper H, Hemminghaus H-J. PCB-Untersuchungen in Innenräumen. Forschungsbericht 203 61 218/04. UBA Nr. 03/2005; http://www.umweltdaten.de/publikationen/fpdf-l/2943.pdf

[86] Hu X, Adamcakova-Dodd A, Lehmler H-J, Hu D, Kania-Korwel I, Hornbuckle KC, Thorne PS. Time course of congener uptake and elimination in rats after short-term inhalation exposure to an airborne polychlorinated biphenyl (PCB) mixture. Environ Sci Technol 2010; 44: 6893–6900.

[87] Heinzow BGJ, Nohr S, Ostendorp, Kerst M, Körner W. Dioxin-like PCB in indoor air contaminated with difference sources. Organohalogen Compounds 2004; 66: 2470-2476.

highest level corresponds to a German indoor air limit value of 5 pg $TEQ_{WHO1998}/m^3$ recommended by a German EPA Working Group in 2007.[88]

4.7 Effects of ventilation and cleaning on indoor air levels

Permanent and temporary ventilation decrease PCB levels indoors by substituting highly polluted indoor air with less polluted with PCB. However, if or when this ventilation activity ceases the PCB concentration in the air will increase slowly again to approach the saturation points. If the source is not removed, there will be enough PCB in the source to sustain the PCB saturation concentration for the lifetime of the building. Efficient cleaning of surfaces, furniture and other equipment may remove PCB in dust and surface films, and thus decrease the PCB in air for a while but not permanently.

In a Danish report from 2011 it was recommended that preliminary preventive actions of careful cleaning, improved ventilation and installation of air cleaners were introduced in the period from the discovering the PCB problem, and until it could finally be solved.[89] More preventive actions are already discussed on page 32.

Another Danish study showed that PCB levels in indoor air in a contaminated apartment was reduced 2-3 fold by frequent vacuuming, dusting off and washing the floor, however, airing out with open windows had no effect.[90] This study also showed that direct removal of the PCB sealing without other arrangements resulted in higher PCB concentration in the indoor air. Cleaning combined with ventilation decreased the indoor PCB levels but did not sufficiently lower levels to below 300 ng/m^3 (see Figure 4.9):

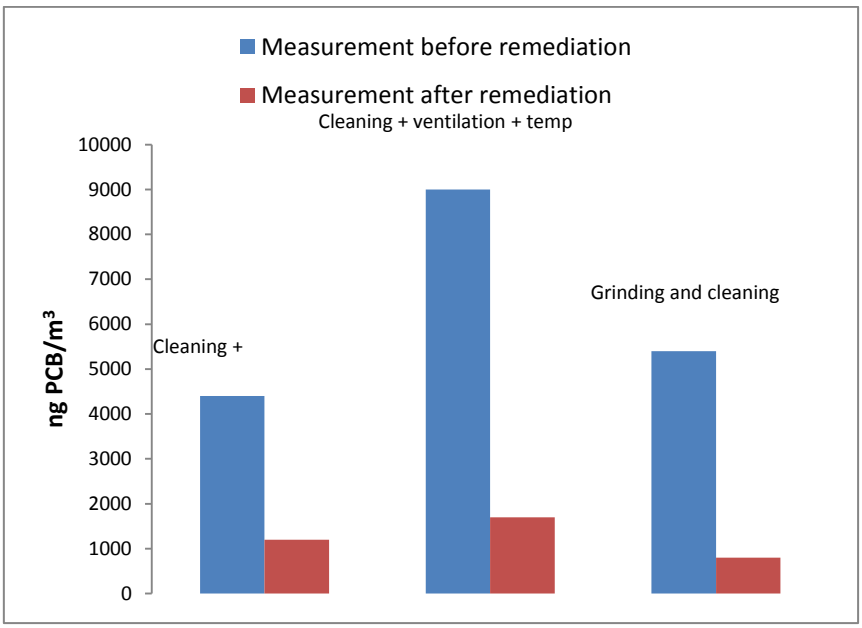

Figure 4.9: Effect of cleaning combined with ventilation and others (Haven and Langeland 2011).

[88] Volland G, Schilling B, Gabrio T, Link B, Zöllner I. Dioxinähnliche polychlorierte Biphenyle (PCB) in der Innenraumluft. Gefahrstoffe – Reinhaltung der Luft 2009; 69: 83-89.
[89] Haven R, Langeland M. Afhjælpningstiltag ved forhøjede PCB-niveauer i indeklimaet. Erhvervs- og Byggestyrelsen og Socialministeriet, marts 2011. http://pcb-guiden.dk/file/159799/pcb_afhjaelpningstiltag.pdf
[90] Frederiksen M, Meyer HW, Ebbehøj NE, Gunnarsen L. Polychlorinated biphenyls (PCBs) in indoor air originating from sealants in contaminated and uncontaminated apartments within the same housing estate. Chemosphere 2012;89: 473-479

5. PCB in people

When PCB is emitted into the environment it dilutes and spreads widely. Because of its persistent nature and long residence time in the environment, levels will continue to build up. The low water solubility means that most PCB in the aquatic environment will stay in sediments, from where small amounts continuously can be released to saturate the water phase.

PCB can directly be taken up and accumulates in organisms living in the sediment or water. More important is, however, the biomagnification of PCB through the food chains, which can result in very high levels in the fatty tissues of organism in the top of the food chain, such as birds of prey, marine mammals and humans.

Everyone in modern society is exposed to background levels of PCB through food and has PCB accumulation in their bodies. People consuming fish products caught in polluted waters, for instance the Baltic Sea, can have higher PCB body burden. Populations in arctic areas may have even higher exposure to PCB, because of their special diet of marine mammals. Fortunately, their exposures have been decreasing in most areas during the last decades.

The chemical and biological fate of PCB differs among the single PCB congeners, and during the transfer through the food chain some congeners will increase in relative abundance and other decrease. Thus, the PCB patterns change from the complex one in the commercial mixtures and to a more simple pattern of the most persistent and bioaccumulative congeners in humans.

5.1 Human background exposures to PCB

The general adult population, without occupational exposure or indoor air exposure to PCB, will mainly be exposed to PCB via intake of PCB-contaminated foodstuffs, mainly in fatty fish, meat and dairy products. In such cases it is often estimated that 80-90% of the PCB intake is from foods.

The European Food Safety Authority (EFSA) has formed an advisory Panel on Contaminants in the Food Chain. This Panel has published the opinion that the six EU indicator congeners (PCB28, PCB52, PCB101, PCB138, PCB153 and PCB180) are representative and convenient to use for analysis and risk assessments. They have estimated that the levels of these 6 congeners correspond to about 50 % of the total PCB content in foodstuff.[91]

However, in Denmark we have had a tradition for analyzing and quantifying PCB_{10} (PCB28, PCB31, PCB52, PCB101, PCB105, PCB118, PCB138, PCB153, PCB156 and PCB180) in foodstuffs, and sometimes in the Nordic countries the single and very abundant congener PCB-153 has been used alone as indicator for PCB.[92]

PCB in foods

In a Danish study the average PCB contents in lamb, chicken, pork and beef meat were respectively 3.4, 5.4, 5.9 and 6.6 µg PCB_{10}/kg fat. In milk, cheese and butter the average levels were respectively 4.4, 6.8, and 1.5 µg PCB_{10}/kg fat. The average concentration in eggs was 4.7 µg PCB_{10}/kg fresh weights. Also fish levels were

[91] EFSA Panel on contaminants in the food chain (CONTAM). Scientific opinion on the risk to public health related to the presence of high levels of dioxins and dioxin-like PCBs in liver from sheep and deer. EFSA Journal 2011; 9:2297

[92] Fromberg A, Granby K, Højgård A, Fagt S, Larsen JC. Estimation of dietary intake of PCB and organochlorine pesticides for children and adults. Food Chemistry 2011; 125: 1179-1187.

reported in fresh weights for herring, salmon, eel, mackerel and Greenland halibut were respectively 15.8, 15.8, 56, 10, 14.9 µg PCB_{10}/kg fresh weight.[93]

The levels of NDL-PCB in Herrings from the Baltic Sea were twice the levels in the North Sea (20 versus 10 ng/g). Cod liver has the highest levels but these have decreased during the last decades.[94]

In Greenland many aquatic food items have been analyzed in connection with AMAP programs. In Table 5.1 shows some of these results.[95] The data illustrates that livers and blubber are the most contaminated:

Table 5.1: PCB (ng/g fresh weight) in various wildlife food items from West Greenland (Johansen *et al*. 2009).

Species	Tissue	No. of samples	Lipid %	PCB_{10}
Lamb	Muscle	5	1.9	0.7
	Liver	5	10	2.0
	Kidney	5	3.2	0.5
	Fat	5	86	1.9
Salmon	Muscle	10	11	8.2
	Liver	5	8.8	2,1
Cod	Muscle	9	0.7	1.5
	Liver	5	59	39
Halibut	Muscle	10	9.4	18
	Liver	5	34	492
Ringed seal	Muscle	20	27	12
	Liver	5	51	8.6
	Kidney	5	10	2.6
	Blubber	10	92	287

Food PCB intake

More than 90% of the NDL-PCB exposure in the general population is via food.[96] Average daily dietary intake in the EU of total NDL-PCB, which corresponds to 3xPCB_3, 2xPCB_6, and 1.7xPCB_7, was estimated to be in the range of 10-45 ng PCB/kg body weight in adults, corresponding to 0.6-2.7 µg/day for a person weighing 60 kg. In general, children had exposure levels 2.5 fold higher than adults, and there were subpopulations with large intakes of contaminated fish or sea mammals and daily intakes above 80 ng PCB/kg b. w. Breastfed infants are a group with a high NDL-PCB intake which might be two orders of magnitude higher than adult exposure. In another EFSA report the background daily food intake of PCB_6 in the EU has been estimated to between 5 and 27 ng/kg b. w.[97]

In Denmark for the years 1993-1997 and 1998-2003, respectively, an average food intake of 2.2 µg PCB_{10}/day and 0.9 µg PCB_{10}/day have been estimated.[98] This estimation of total PCB was done on the basis

[93] Fromberg A, Granby K, Højgård A, Fagt S, Larsen JC. Estimation of dietary intake of PCB and organochlorine pesticides for children and adults. Food Chemistry 2011; 125: 1179-1187.
[94] Chemical contaminants, Food monitoring 2004-2011. National Food Institute, Technical University of Denmark, 2013.
[95] Johansen P, Muir D, Asmund G, Riget F. Contaminants in the traditional Greenland diet – Supplementary data. NERI Technical Report No. 704, 2009.
[96] EFSA (European Food Safety Authority). Opinion of the Scientific Panel on Contaminants in the food chain on a request from the Commission related to the presence of non dioxin-like polychlorinated biphenyls (PCB) in feed and food. The EFSA Journal 2005; 284: 1-137.
[97] EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on the risk to public health related to the presence of high levels of dioxins and dioxin-like PCBs in liver from sheep and deer. EFSA Journal 2011;9:2297.
[98] Fromberg A, Granby K, Højgård A, Fagt S, Larsen JC. Estimation of dietary intake of PCB and organochlorine pesticides for children and adults. Food Chemistry 2011; 125: 1179-1187.

of analytical results of PCB-153 and multiplication with a factor of 9. The distribution of results is shown in Figure 5.1: [99]

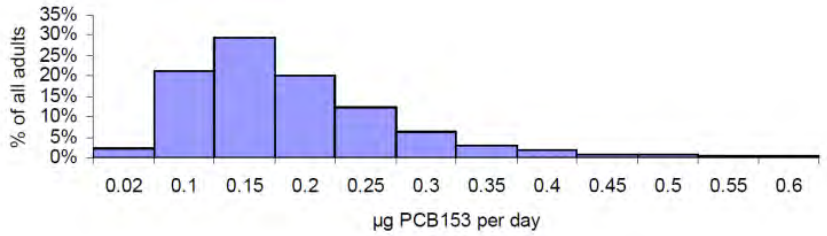

Figure 5.1: Daily intake of PCB153 (µg per day), distribution for adults (Fromberg et al. 2006).

The two largest contributions to the intake of the PCB were from fish and meat (see Figure 5.2):

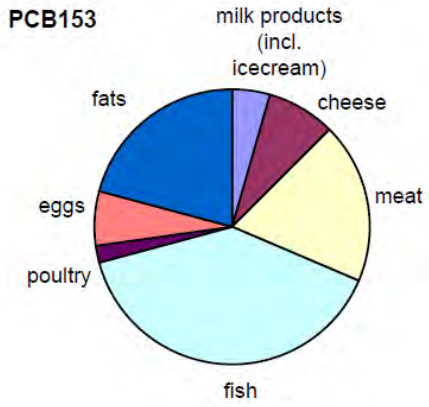

Figure 5.2: Adults, estimated contributions of various food groups to intakes of PCB153 (Fromberg et al. 2006).

In 2013 the mean daily exposure to dioxins and DL-PCB was estimated at 0.87 pg-TEQ_{WHO}/kg bw, and the mean daily exposure to PCB_6 was estimated at 1.8 ng/kg bw (max. 16.4 ng/kg bw) for the total Danish population and 2.7 ng/kg bw (max. 12.5 ng/kg bw) for children aged 4 to 14. This is much lower than previously estimated but PCB_6 has to be multiplied with a factor 2-5 to get total PCB. In comparison, the average daily PCB intake in Western Greenland is much higher, and it has been estimated to 23 µg PCB_{10}/person.[100]

Limit values

In experiments with Rhesus monkeys receiving daily doses of Aroclor 1254 for several months a dose-related increase in liver weight occurred, and there were decreases in the IgG and IgM immunoglobulin response to a sheep red blood cell challenge. A lowest observable adverse effect level (LOAEL) of 0.005 mg/kg body weight per day was determined. Applying an uncertainty factor of 300 a Tolerable Daily Intake (TDI) of 20 ng/kg bw/day was derived by WHO for mixtures of PCBs.[101] In regards to dioxins-like PCBs, in 2001 the EU established a Tolerable Weekly Intake (TWI) of 14 pg TEQ_{WHO}/kg bw. Furthermore, in 2007, the

[99] Fromberg A, Granby K, Højgård A, Fagt S. Intake of PCB from fatty foods. Organohalogen Compounds 2006; 68: 1509-1512.
[100] Johansen P, Muir D, Asmund G, Riget F. Contaminants in the traditional Greenland diet. NERI Technical Report No. 492, 2004.
[101] Concise International Chemical Assessment Document 55. Polychlorinated biphenyls: human health aspects. Geneva: WHO, 2003. http://www.who.int/ipcs/publications/cicad/en/cicad55.pdf

French Food Safety Agency proposed a TDI of 10 ng/kg bw/day for NDL-PCB_6 and 20 ng/kg bw/day for NDL-PCB_{10}.[102]

Previously, the EU has established maximum levels in food for dioxins and DL-PCBs, and in 2012 also for the sum of the six indicator NDL-PCBs (PCB 28, 52, 101, 138, 153 and 180). Moreover, the EU has introduced action levels for dioxins, DL-PCBs and NDL-PCBs. Foods with levels of dioxins and PCBs above the action levels but below the maximum levels can be marketed, although the EU member state must try to find the cause for the increased levels of dioxins and PCBs. The current (2012) maximum levels and action levels for fish products (wet weight: ww) and other foods (lipid weight: lw) are listed in Tables 5.2 and 5.3:[103]

Table 5.2: Maximum and actions levels for dioxins and PCBs in fish and fish products, fruits, vegetables and cereals, and foods for infants and young children (DTU Food 2013).

Food	**Action levels**		**Maximum levels**		
Unit	pg TEQ_{WHO}/g ww		pg TEQ_{WHO}/g ww		ng/g ww
	Dioxins	+ DL-PCB	Dioxins	+ DL-PCB	PCB_6
Muscle meat of fish	1.5*	2.5*	3.5	6.5	75
Muscle meat of wild fresh water fish	-	-	3.5	6.5	125
Muscle meat of wild caught eel	-	-	3.5	10	300
Marine oils	-	-	1.75	6.0	200
Fish liver	-	-	-	20	200
Fruits, vegetables and cereals	0.3	0.1	-	-	-
Foods for infants and young children	-	-	0.1	0.2	1.0

*Action levels only apply for farmed fish.

Table 5.3: Maximum and action levels for dioxins and PCBs in meat, dairy products and fats (DTU Food 2013).

Food	Action levels		Maximum levels		
Unit	pg TEQ_{WHO}/g lw		pg TEQ_{WHO}/g lw		ng/g lw
	Dioxins	+ DL-PCB	Dioxins	+ DL-PCB	PCB_6
Meat and fat of bovine animal and sheep	1.75	1.75	2.5	4.0	40
Meat and fat of pigs	0.75	0.5	1.0	1.25	40
Meat and fat of poultry	1.25	0.75	1.75	3.0	40
Mixed animal fat	1.0	0.75	1.5	2.5	40
Liver of terrestrial animals	-	-	4.5	10.0	40
Raw milk and dairy products	1.75	2.0	2.5	5.5	40
Hen eggs and egg products	1.75	1.75	2.5	5.0	40
Vegetable oils and fats	-	-	0.75	1.25	40

There is an older Danish guideline dating back to 1999 for acceptable levels of PCB in fish oils of 100 ng PCB153 or 400 ng PCB_{10}/g fresh weight in fish and lipid weight in other foodstuffs.[104]

The U.S. Food and Drug Agency (FDA) also established limit values for PCB in various food items. For example 0.2 ppm PCB in infant food, 0.3 ppm in eggs, 1.5 ppm (lipid basis) in milk and other dairy products, 2 ppm (lipid basis) in eatable parts of fish and shellfish and 3 ppm (lipid basis) in poultry and red meat.

Dietary exposure in Denmark to dioxins and DL-PCB as well as to NDL-PCB exceeds the TDI/TWIs by a small fraction in the population, and mainly for children.[105]

[102] Cited from: Chemical contaminants, Food monitoring 2004-2011. National Food Institute, Technical University of Denmark, 2013.
[103] Chemical contaminants, Food monitoring 2004-2011. National Food Institute, Technical University of Denmark, 2013.
[104] Johansen P, Muir D, Asmund G, Riget F. Contaminants in the traditional Greenland diet. NERI Technical Report No. 492, 2004.

5.2 PCB accumulation in humans

Human body burden with PCB can be influenced by a number of factors, such as:

- Diet and consumption habit
- Age
- Body weight changes
- Nursing status
- Time of sampling
- Analytical method

PCB circulates and accumulates in the body associated with lipids and lipoproteins. The highest concentrations of PCB occur in fat-rich tissues like adipose tissue and human milk.[106] At "steady-state" where the rate of uptake and rate of elimination of PCB are the same, the PCB concentration will approximately be the same in blood, muscle, adipose and milk, if the levels are reported on lipid basis.[107] Though the levels of PCB in fats are about the same, adipose tissue has much higher fat % (about 80 %) and can contain 300-fold more PCB than the blood serum/plasma (lipid content about 0.3 %) and in that way regulate and dilute the blood-PCB. Mature human milk has a fat % of about 3.5 % while colostrum only contains 1-2 % lipids.

Biological monitoring can be undertaken in various tissues depending on, which are most convenient. Since the human intake of PCB in praxis will not be constant, there may be small differences in PCB lipid levels between tissues. A single meal with PCB polluted food or other acute exposures will increase blood PCB for a while, until the PCB has been distributed throughout the entire body and a new equilibrium has been obtained. Such short-term exposures will not significantly change the PCB levels in the adipose tissues, which reflect life-long exposure to PCB from many sources.[108]

Many studies have confirmed that more than 60 % of the PCB in human tissues consists of the seven PCB congeners: PCB28, PCB74, PCB118, PCB138, PCB153, PCB170 and PCB180. Most abundant is PCB-153 with 10-30 % of the total content, and when using a multiplication factor of 5-6 the total content in lipid can be estimated.[109]

In earlier studies using the pure analytical separation by packed columns and comparison with commercial mixtures quantitation was done based on a selection of two to eleven major peaks. Results with two peaks gave two-fold higher results than with 8 or 11 peaks.[110,111]

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[105] Chemical contaminants. Food monitoring 2004-2011. National Food Institute, Technical University of Denmark, 2013.
[106] Jensen AA. Polychlorobiphenyls (PCBs), polychlorodibenzo-pdioxins (PCDDs) and polychlorodibenzofurans (PCDFs) in human milk, blood and adipose tissue. Sci Total Environ 1987; 64: 259-293.
[107] Brown JF, Lawton RW. Polychlorinated biphenyls (PCB) partitioning between adipose tissue and serum. Bull Environ Contam Toxicol 1984; 33: 277-280.
[108] Bekanntmachung des Umweltbundesamtes. Abschätzung der zusätzlichen Aufnahme von PCB in Innenräumen durch die. Bestimmung der PCB-Konzentrationen in Plasma bzw. Vollblut. Stellungnahme der Kommission „Human-Biomonitoring" des Umweltbundesamtes. Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz 2003; 46: 923-927.
http://www.umweltdaten.de/gesundheit/monitor/PCB-Innenraum-HBM.pdf
[109] Longnecker MP, Wolff MS, Gladen BC, Brock JW, Grandjean P, Jacobson JL, Korrick SA, Rogan WJ, Weisglas-Kuperus N, Hertz-Picciotto I, Ayotte P, Stewart P, Winneke G, Charles J, Jacobson SW, Dewailly E, Boersma ER, Altshul LM, Heinsow B, Pagano JJ, Jensen AA.. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ Health Perspect 2003; 111: 65-70.
[110] Jensen AA: Polychlorobiphenyls (PCBs), polychlorodibenzo-pdioxins (PCDDs) and polychlorodibenzofurans (PCDFs) in human milk, blood and adipose tissue. Sci Total Environ 1987; 64: 259-293.

Generally speaking, the concentration of PCB in the body will increase by age, because the daily intake in most cases is larger than the elimination. Furthermore, PCB is very long-lived in the body. The half-lives in workers of the low chlorinated congeners are from days to 6 years, while the half-lives for congeners with more than 4 chlorines can be 8-24 years.[112] Not only the chlorine content but also the particular structure and doses are important for the half-lives.

Selected examples of elimination half-lives in humans for some congeners obtained from intoxications and experiments with volunteers are shown in Table 5.4:

[111] Longnecker MP, Wolff MS, Gladen BC, Brock JW, Grandjean P, Jacobson JL, Korrick SA, Rogan WJ, Weisglas-Kuperus N, Hertz-Picciotto I, Ayotte P, Stewart P, Winneke G, Charles J, Jacobson SW, Dewailly E, Boersma ER, Altshul LM, Heinsow B, Pagano JJ, Jensen AA.. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ Health Perspect 2003; 111: 65-70.
[112] Wolff MS, Fischbein A, Selikoff IJ. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ Res 1992; 59: 202-216.

Table 5.4: Examples of elimination half-lives for PCB congeners in humans.

PCB congener	Elimination half-life in humans (years)								
	Ref [113]	Ref [114]	Ref [115]	Ref [116]	Ref [117]			Ref [118]	Ref [119]
					Japan	Yusho	YuCheng	Children	
PCB28		1.4	4.8	5.6					4.5
PCB52			5.5	2.6					1.3
PCB77	0.1				0.07-0.7				
PCB81	0.7				0.7-1.7				
PCB101									2.8
PCB105	2.4	3.9		5.2	2.4-5.2			5.4	
PCB114	10				10-25				
PCB118	3.8	5.8	9.6	9.3	3.8-6.3	17.6	1.7	5.7	
PCB123	7.4				4.2-12				
PCB126	1.6				1.5-4.5				
PCB138		7	16.3	10.8		15.2	4.8	3.7	
PCB153		12.4		14.4		10.6	3.9	8.4	
PCB156	16				16-38	13.4	4.9	7.6	
PCB157	18				12-27				
PCB167	12				8.4-12				
PCB169	7.3				7.3-13	10	10		
PCB170				15.5		14.7	5.5	7.6	
PCB180			9.9	11.5		14.9	5.4	9.1	
PCB187				10.5				8.0	
PCB189	22				5.4-41				

Pregnant women are a significant exception to the rule, when it comes to PCB excretion, as each mother transfers some of her body burden on to the fetus. Women who breast feed excrete and transfer to the infant a considerable amount of the stored PCB with mothers' milk. That explains that women, in general, have lower PCB levels in adipose tissues than men.[120]

5.3 PCB levels in adipose tissue

Adipose tissue is approximately 80% fat and has the highest PCB concentration and contains most of the PCBs in the body. As mentioned, based on fat content the levels will be similar to other body tissues, and the average background concentration of total-PCB in industry countries is mostly between 0.5 and 1 ppm (mg/kg lipid). Previously, the most studied adipose tissue was from deceased people which are not

[113] Milbrath MO, Wenger Y, Chang CW, Emond C, Garabrant D, Gillespie BW, Jolliet O. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ Health Perspect 2009; 117: 417–425.
[114] Brown JF, Lawton RW, Ross MR, Feingold J, Wagner RE, Hamilton SB. Persistence of PCB congeners in capacitor workers and Yusho patients. Chemosphere 1989; 19: 829–834.
[115] Wolff MS, Fischbein A, Selikoff IJ. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ Res 1992; 59: 202–216.
[116] Ritter R Scheringer M, MacLeod M, Moeckel C, Jones KC, Hungerbühler K. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. Environ Health Perspect 2011; 119:225–231.
[117] Ogura I. Half-life of each dioxin and PCB congener in the human body. Organohalogen Compounds 2004; 66: 3329–3337.
[118] Grandjean P, Budtz-Jørgensen E, Barr DB, Needham LL, Weihe P, Heinzow B. Elimination half-lives of polychlorinated biphenyl congeners in children. Environ Sci Technol 2008; 42: 6991–6996.
[119] Schettgen T, Alt A, Preim D, Keller D, Kraus T. Biological monitoring of indoor-exposure to dioxin-like and non-dioxin-like polychlorinated biphenyls (PCB) in a public building. Toxicol Lett 2012; 213: 116-124.
[120] Jensen AA, Slorach SA. Chemical Contaminants in Human Milk. Boca Raton: CRC Press, 1991.

representative for the general population. In later years methods for sampling of adipose from living people have improved.

A recent Danish study determined the levels of certain PCB congeners (PCB99, PCB118, PCB138, PCB153, PCB156, PCB170, PCB180, PCB183, PCB187 and PCB201) in adipose tissue (average age: 56 years; 126 males; 119 females).[121] Levels in the city of Aarhus were lower than in the larger Copenhagen municipality. Lifetime lactation, BMI and consumption of fruit, vegetables, and dairy products were inversely associated, while age and consumption of fish were positively associated with higher levels. The median PCB concentrations in men and women were 1.05 mg/kg lipid and 0.98 mg/kg lipid, respectively.

5.4 PCB levels in human blood

In human blood PCB binds to lipoproteins and thus is mainly found in the plasma/serum fraction. The total PCB concentration is normally less than 2 ppb (µg/L) fresh weight but 5-50 fold higher levels have been measured in blood from exposed workers and Yusho/YuCheng victims.[122]

During pregnancy PCB levels in blood gradually increase to about two fold previous levels but the levels decreases again after delivery.[123] PCB in cord blood is much lower than in maternal blood but it can be partly explained with a lower lipid content of cord blood. In most studies PCB in blood increases with age and fish consumption, and levels in males are higher than in females.

In the Faroe Islands the highly chlorinated PCBs in placenta and cord tissue correlated with the PCB in maternal serum.[124]

In the National Health and Nutrition Examination Survey (NHANES) 1999-2010 in the USA a lot of data on 37 PCB congeners in blood serum from the US population have been collected. The congeners included were: PCB44, PCB49, PCB110, PCB101, PCB52, PCB149, PCB87, PCB28, PCB128, PCB151, PCB66, PCB189, PCB99, PCB105, PCB118, PCB74, PCB138/158, PCB195, PCB183, PCB153, PCB146, PCB177, PCB187, PCB170, PCB180, PCB172, PCB196/203, PCB157, PCB156, PCB178, PCB206, PCB167, PCB194, PCB209 and PCB199. The 2003-2004 data from approximately 2000 individuals have been used to evaluate the persistence of the various congeners in humans. Of these congeners PCB 28, PCB52, PCB74, PCB118, PCB138, and PCB153 were detected in all samples, and PCB44, PCB47, PCB66, PCB99, PCB101, PCB105, PCB110, PCB146, PCB149, PCB170, and PCB187 were present in almost all samples. The highest mean levels were: PCB153> PCB180 > PCB138 > PCB118 > PCB170 > PCB187 > PCB74 > PCB99 > PCB199 > PCB28 > PCB194 > PCB156 > PCB196 > PCB206 > PCB146 > PCB52 etc. The less-chlorinated PCBs did not correlate to being less persistent; for example PCB28 was more persistent than PCB101 and PCB110. The structural pattern is also important. Congeners with chlorine atoms in the 2,5- and 2,3,6-positions appear to be more susceptible to

[121] Bräuner EV, Raaschou-Nielsen O, Gaudreau E, LeBlanc A, Tjønneland A, Overvad K, Sørensen M. Predictors of polychlorinated biphenyl concentrations in adipose tissue in a general Danish population. Environ Sci Technol 2011; 45: 679-685.
[122] Jensen AA. Background levels in humans. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.
[123] Kodama H, Ota H. Transfer of polychlorinated biphenyls to infants from their mothers. Arch Environ Health1980; 35: 95 -100.
[124] Needham LL, Grandjean P, Heinzow B, Jorgensen PL, Nielsen F, Patterson DG, Sjödin A, Turner WE, Weihe P. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ Sci Technol. 2011; 45: 1121–1126.

biotransformation, whereas congeners with chlorine atoms in the 2,3,4-, 2,4,5-, 3,4,5- and 2,3,4,5-positions appear to be more persistent.[125]

5.5 Levels of PCB in blood from dwellers and other exposed indoors

In a Swedish study PCB in blood from 21 dwellers living in apartments with PCB-sealants were compared to blood samples of 15 persons in apartments without PCB. The median concentration based on the sum of 30 PCB congeners was 434 ng PCB/g lipids in people from contaminated apartments and 226 ng PCB/g lipids in the controls. The congener pattern was different because the most abundant congeners in the controls were PCB153, PCB180, and PCB138, while in the exposed people PCB28, PCB180, PCB153 and PCB138 dominated and PCB28 was 30 fold higher than in controls.[126]

In Germany there have been some studies done on the relation between PCB levels in indoor air in schools and PCB levels in blood of the teachers and pupils. In most studies, where sealants were the PCB source, the levels of PCB 28 and PCB52 more than doubled but besides PCB101 the concentrations of the higher congeners were not significantly different, and in total there was only a moderate increase in total PCB_6 in the blood of the exposed persons, which was about 2 µg/L.[127,128] These two investigations underplay the actual situation. They lack separate concentration of PCB52 in the blood, although it is the most abundant congener measured by them in the indoor air. The reason was that they were not able to analyze PCB52 in the blood. This result poses a question to their ability to analyze PCB congeners in blood. Therefore, the results are incomplete, and the conclusions are premature.

In another later study by the same authors PCB52 was measured in the blood but the levels were 3-4 folds lower than PCB28.[129] Thus analytical problems may still be present. The single blood samples from the exposed and unexposed teachers were pooled each in two samples. The range of levels in exposed teachers was missing, thus it is not clear if some of the exposed were not so exposed.

Daily exposure to 1000 ng PCB/m^3 in indoor air in another German study only resulted in an increase of 3% of the PCB_6 in blood.[130]

In addition, in a German high school with high indoor PCB contamination from PCB flame-retarded acoustic plates, the blood levels in teachers and pupils of the low-chlorinated PCB28 and PCB52 were not increased but levels of PCB138, PCB153 and PCB180 were increased 3-18 fold.[131]

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[125] Megson D, O'Sullivan G, Comber S, Worsfold PJ, Lohan MC, Edwards MR, Shields WJ,. Sandau CD, Patterson DG Jr. Elucidating the structural properties that influence the persistence of PCBs in humans using the National Health and Nutrition Examination Survey (NHANES) dataset. Science Total Environment 2013; 461–462: 99–107.

[126] Johansson N, Hanberg A, Wingfors H, Tysklind M. PCB in building sealant is influencing PCB levels in blood of residents. Organohalogen Compounds 2003; 63: 381-384.

[127] Volland G, Schilling B, Gabrio T, Link B, Zöllner I. Dioxinähnliche polychlorierte Biphenyle (PCB) in der Innenraumluft. Gefahrstoffe – Reinhaltung der Luft 2009; 69: 83-89.

[128] Gabrio T, Piechotowski I, Wallenhorst T, Klett M, Cott L, Friebel P, Link B, Schwenk M. PCB-blood levels in teachers, working in PCB-contaminated schools. Chemosphere 2000; 40: 1055-1062.

[129] Schwenk M, Gabrio T, Päpke O, Wallenhorst T. Human biomonitoring of polychlorinated biphenyls and polychlorinated dibenzodioxins and dibenzofuranes in teachers working in a PCB-contaminated school. Chemosphere 2002; 47: 229-233.

[130] Kalberlah F, Schulze J, Hassauer M, Oltmanns J. Toxikologische Bewertung polychlorierter Biphenyle (PCB) bei inhalativer Aufnahme. Materialien 62. Essen: Landesumweltamt NRW, 2002.

[131] Köster D. Während einer Schulsanierung erhobene PCB-Blutwerte bei Lehren und Schülern – eine vergleichende Untersuchung. Umwelt Medizin Ges 2001; 14: 301-304.

In a German primary and secondary school in Nuremburg contaminated by PCB (6 DIN congeners x 5) the indoor air levels were between 690 and 20 800 ng/m^3 with a median of 2044 ng/m^3.[132] The congener data is shown in Table 5.5:

Table 5.5: PCB congeners in indoor air in a PCB contaminated German schools (Liebl *et al.* 2004).

PCB congener	Range ng/m^3	Median ng/m^3
PCB28	4-600	33
PCB52	38-2300	293
PCB101	3-1100	66
PCB138	<80	4
PCB153	<80	5
PCB180	<80	1.6

In both PCB contaminated and non-contaminated schools PCB 138, 153 and 180 were detectable in all blood plasma samples from pupils. PCB28, 52 and 101 were detectable in most blood samples from pupils from contaminated schools but only in a few of the samples from non-contaminated schools. The median of the sum of these three PCB congeners in contaminated schools was 22 ng/L blood but <1 ng/L in controls.

In a recent German study of a public building in Achen indoor air monitoring revealed high concentrations of lower chlorinated PCB emitted from elastic joint sealing (see Table 5.5):[133]

Table 5.6: PCB in indoor air of a public building in Achen, Germany (Schettgen *et al.* 2012).

ng/m^3	PCB28	PCB52	PCB101	PCB138	PCB153	PCB180	ΣPCBx5
Median	140	160	29	3	2	<1	1740
95th percentile	320	348	86	22	13	2	3740
Max. value	450	470	150	31	21	3	4280

Blood plasma samples from 209 of the employees working in the building were analyzed for the 6 indicator PCBs and 12 dioxin-like PCBs. Only levels for PCB28, PCB52 and PCB101 of the indicator PCBs were higher than controls, and only two of the DL-PCBs were significant higher (Table 5.7):

Table 5.7: PCB in blood plasma from exposed employees (Schettgen et al. 2012).

µg/L plasma	PCB28	PCB52	PCB101	PCB138	PCB153	PCB180	PCB105	PCB118	ΣPCB
Median	0.087	0.024	0.012	0.253	0.380	0.279	0.013	0.061	1.109
95th percentile	0.352	0.091	0.046	0.846	1.256	1.085	0.042	0.187	-
Max. value	0.878	0.426	0.123	2.226	3.360	3.179	-	-	

In the exposed employees the median concentration of the sum of PCB28, PCB52 and PCB101 in blood plasma was 123 ng/L compared to <10 ng/L for controls, thus more than ten times higher. About the same relation was observed for the maximum values.

[132] Liebl B, Schettgen T, Kerscher G, Broding H-C, Otto A, Angerer J, Drexler H. Evidence for increased internal exposure to lower chlorinated polychlorinated biphenyls (PCB) in pupils attending a contaminated school. Int J Hyg Environ Health 2004; 207: 315-324.
[133] Schettgen T, Alt A, Preim D, Keller D, Kraus T. Biological monitoring of indoor-exposure to dioxin-like and non-dioxin-like polychlorinated biphenyls (PCB) in a public building. Toxicol Lett 2012; 213: 116-124.

There was no relationship between indoor air measurements and internal exposure of the employees in the corresponding office, but estimated lifetime exposure of the employees from the building turned out to be a significant factor for plasma levels of PCB 28.

A recent study in Boston, MA, USA, the blood from 18 teachers working in PCB-contaminated schools were analyzed for 57 individual PCB congeners, which included more of the lower chlorinated congeners than the 35 congeners measured in the NHANES projects.[134] The results for 33 congeners were compared between the two studies (Table 5.8):

Table 5.8: Comparison of data on PCB in blood in NHANES and PCB exposed teachers in Boston (Herrick *et al.* 2011).

Group	PCB (sum of 33 congeners) in blood median ng/g (ppb)
Boston teachers, age 33-64	1.32
2003-2004 NHANES, age 33-64	1.11
Boston teachers, age 50-64	2.14
2003-2004 NHANES, age 50-64	1.49

The levels of PCB in in the teachers' blood were generally higher in one of the schools. PCB congener 47 contributed substantially to these elevated levels. Levels of the highly-chlorinated congeners increased with the age of the teacher but not the low-chlorinated. For the young teachers the low-chlorinated congeners (PCB 6 to PCB74) made a greater contribution to the overall total serum PCB levels. Comparing the teachers to the referent population of men from the Greater Boston area (all under age 51), no difference in total serum PCB levels was observed between the referents and teachers up to 50 years age. However, the teachers had significantly elevated serum concentrations of lighter congeners (PCB 6 to PCB74).

A study found an association between PCB in indoor air and in blood serum among older residents of upper Hudson River communities.[135] This area is in the neighborhood of industrial facilities, which have produced electrical PCB capacitors during the years 1945 to 1977, and which have emitted large but unknown amounts of PCB into the air, and contaminated the villages around them with PCB. In addition, from 1945-1977 these facilities released 500 tons PCB into the Hudson River. In these small towns the total sum of the 12 congeners: PCB28, PCB74, PCB99, PCB105, PCB118, PCB153, PCB170, PCB180, PCB183, PCB187 and PCB194 (*without correction factor!)* was measured in indoor air samples from 176 homes in the area. The mean level was 14 ng PCB/m^3, which were more than 20 fold higher than the previously measured PCB levels in ambient air. These levels were, however, even if multiplied with a correction factor, low and indicated that there was no specific indoor PCB source in these homes. The results indicated a significant correlation between levels of the two congeners: PCB28 and PCB105 in indoor air of homes, and the levels of these congeners in blood serum from 170 residents aged 55-74 years. In persons, who had lived in their homes for more than 39 years this significant correlation also was found for ΣPCB. The mean PCB concentration in blood serum was determined to 549 ng PCB/g lipid without using correction factor. This very high mean serum level indicated presence of other sources such as background-polluted local foods or general surface contamination in the area caused by the long-term emissions from the nearby industry.

[134] Herrick RF, Meeker JD, Altshul L. Serum PCB levels and congener profiles among teachers in PCB-containing schools: a pilot study. Environmental Health 2011; 10: 56. http://www.ehjournal.net/content/10/1/56

[135] Fitzgerald EF, Shrestha S, Palmer PM, Wilson LR, Belanger EE, Gomez MI, Cayo MR, Hwang SA. Polychlorinated biphenyls (PCBs) in indoor air and in serum among older residents of upper Hudson River communities. Chemosphere 2011; 85: 225-231.

In the recent investigation in Farum Midtpunkt the concentrations of PCB_6 (without correction) in blood plasma (fresh weight) from 139 PCB-exposed individuals living in PCB polluted apartments ranged 0.2-16 µg/L with a mean of 3.5 µg/L.[136] The mean concentration of PCB_{27} was about the double at 6.8 µg/L with a range of 0.4-29 µg/L. The means of the controls were respectively 1 and 1.5 µg/L. Thus the exposed had about four fold higher PCB levels than the controls. Females had, as expected probably because of lactation periods, lower levels than men. Also as expected there was a clear increase in PCB levels by age, which may be caused by the longer exposure time and previous higher PCB levels in food. See Figure 5.4:

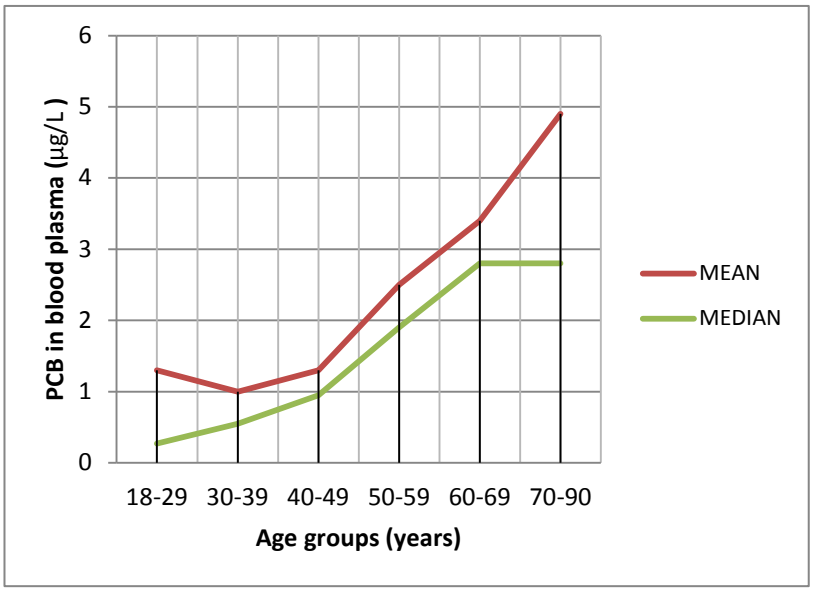

Figure 5.4: Age dependency of PCB in blood plasma from residents of Farum Midtpunkt (Data from SST 2012).

In this study 27 congeners were analyzed in the blood plasma samples.[137] For the 134 non-exposed only PCB 138, 153 and 180 was determined in all samples and 8 of the congeners were not present significantly, while all exposed dwellers for had PCB28, 52, 66, 74, 99, 118, 138, 153, 170, 180 and 187 in the blood and only 5 congeners were absent; thus the exposed are especially exposed to more PCBs and especially to the lower chlorinated congeners. The mean and median values for various PCB groups are shown in Table 5.9.

Table 5.9: Concentration of PCB in blood plasma (µg/L) from Farum Midtpunkt (adapted from Meyer *et al.* 2013).

PCB aggregations	Non-exposed (n=134) (µg/L)		Exposed (n=139) (µg/L)	
	Median	Mean	Median	Mean
Sum of 6 indicator PCBs: PCB 28, 52, 101, 138, 153 and 180	0.81	0.95	2.72	3,45
Sum of 27 congeners	1.26	1.52	4.90	6.82
Sum of 12 dioxin-like PCBs (PCB77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)	0.12	0.15	0.24	0.31
Sum of 15 not dioxin-like PCBs (PCB28, 52, 66, 74, 99,101,138, 153,1790, 178, 180, 182, 183, 187, 190)	1.14	1.37	4.70	6.51

[136] PCB eksponering i Farum Midtpunkt – måling i boliger og blod. København: Sundhedsstyrelsen, 2012.
[137] Meyer HW, Frederiksen M, Göen T, Ebbehøj NE, Gunnarsen L, Brauer C, Kolarik B, Müller J, Jacobsen P. Plasma polychlorinated biphenyls in residents of 91 PCB-contaminated and 108 non-contaminated dwellings – An exposure study. Intern J Hyg Environ Health 2013; 216: 755-762.

The associations between lower-, intermediate- and higher chlorinated PCBs in plasma and exposure time in contaminated apartments were assessed in Figure 5.5, 5.6 and 5.7, respectively:

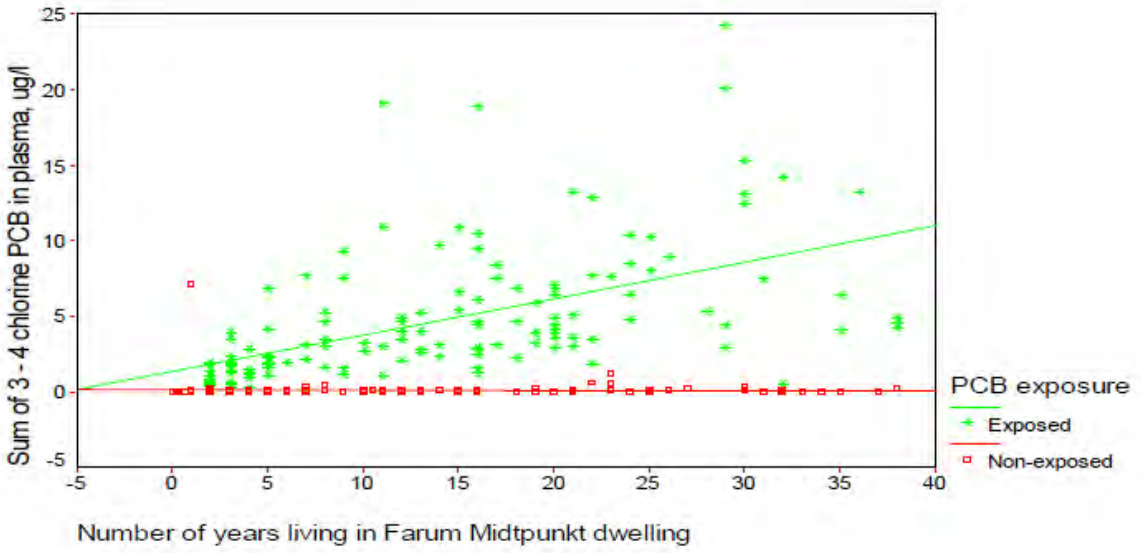

Figure 5.5: Relations of sums of low (tri/tetra) chlorinated PCBs in plasma, versus number of years living in exposed or non-exposed flats (Meyer et al. 2013).

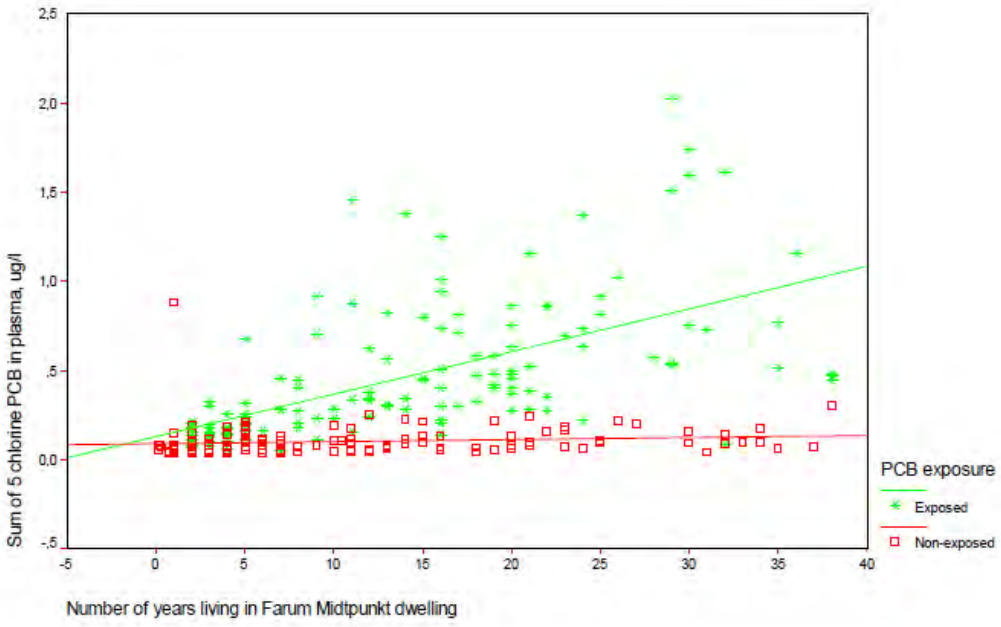

Figure 5.6: Relations of sums of medium (penta) chlorinated PCBs in plasma, versus number of years living in exposed or non-exposed flats (Meyer et al. 2013).

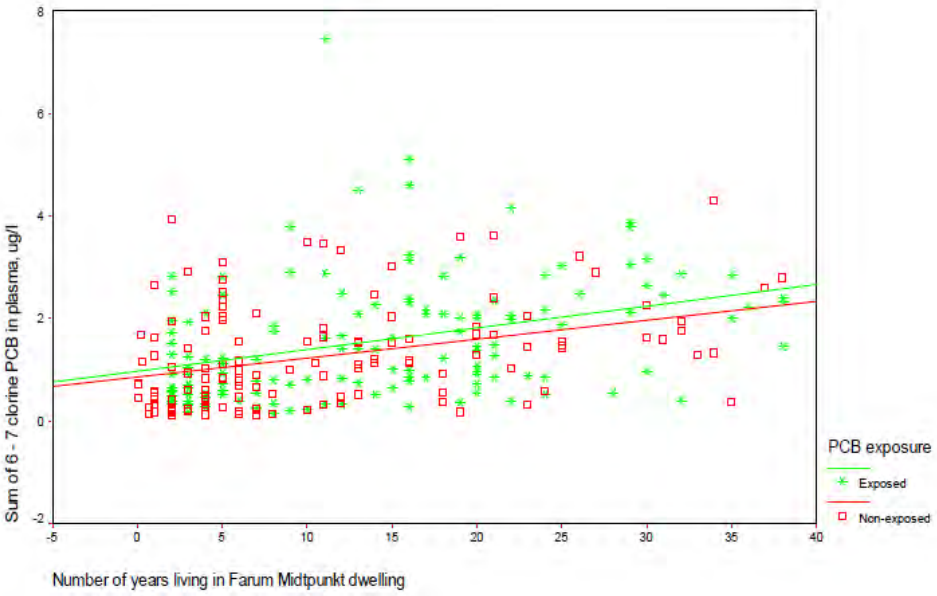

Figure 5.7: Relations of sums of highly (hexa/hepta) chlorinated PCBs in plasma, versus number of years living in exposed or non-exposed flats (Meyer et al. 2013).

Indoor air levels and plasma levels of residents were correlated, especially for the low chlorinated congeners. The relation between PCB28 and sum of 6-7 chlorine PCB in air and blood plasma is shown in Figure 5.8:

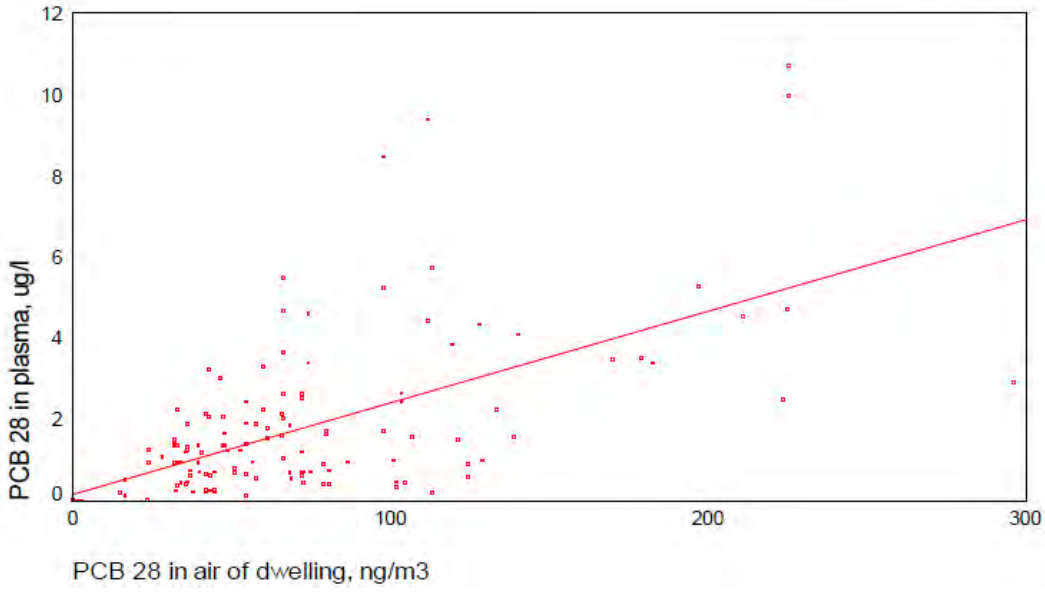

Figure 5.8: Scatter plot of indoor air and dwellers' blood plasma concentrations of PCB 28 in Farum Midtpunkt. N = 154; Spearman correlation coefficient = 0.69; p < 0.001. The formula for the fit line based on Robust Linear Regression: Yi = 0.156 + 0.023Xi + ei (Meyer et al. 2013).

5.6 Levels in human milk

Average concentrations of PCB in human milk fat are typically between 0.5 and 2 ppm (mg/kg) depending on time and place of sampling.[138] Human milk from urban areas has in general higher levels than from rural areas. Milk from a woman occupationally exposed in a capacitor factory contained 10-100 fold more PCB than milk from non-exposed mothers.[139]

The average concentration of PCB in Danish human milk sampled in the 1970s and 1980s was 0.8-2.8 mg/kg lipid. In a later study of samples from 1993-94 the average had decreased to 0.4 mg PCB/kg lipid.[140]

A few of the most persistent and bioaccumulative PCB congeners constitute most of the PCB in human milk. Results from Japan, where 10 congeners made up 95% of the PCB, and from the USA, where 8 made up 65% of the PCBs, are shown in Table 5.10.[141] The difference may be caused by differences in sources and/or analytical methods:

Table 5.10: Most important PCB congeners in human milk (WHO 2003):

Relative PCB congener concentration in human breast milk (%)		
	Japan	**USA**
PCB28	8.4	-
PCB18	2.0	-
PCB70	-	6.6
PCB74	19	-
PCB99	-	4.0
PCB101	2.8	-
PCB105	-	3.7
PCB118	11.8	-
PCB153	15.5	12
PCB138	15.8	7.8
PCB156	-	4.0
PCB157	2.3	-
PCB179	-	9.4
PCB180	-	4.5
PCB183	1.6	-
PCB185	3.2	-

Human studies from Japan have shown that levels of PCB in the blood of breast-fed infants rose gradually with ingestion of breast milk and exceeded their mothers' blood levels after 3 month breast-feeding, and continued to rise the first year before it decreases.[142] This trend has been confirmed for PCB and other POPs in other studies. Results from a German study are shown in Figure 5.9.[143]

[138] Jensen AA, Slorach SA. Chemical contaminants in human milk. Boca Raton: CRC Press, 1991.
[139] Yakushiji T, Watanabe I, Kuwabara K, Yoshida S, Koyama K, Hara I, Kunita N. Long-term studies of the excretion of polychlorinated biphenyls (PCBs) through the mother's milk of an occupationally-exposed worker. Arch Environ Toxicol 1978; 7:493-504.
[140] Indhold af dioxiner, PCB, visse chlorholdige pesticider, kviksølv og selen i modermælk hos danske kvinder 1993-94. København: Sundhedsstyrelsen, 1999.
[141] Polychlorinated biphenyls: human health aspects. Concise International Chemical Assessment Document 55. Geneva: World Health Organization, 2003.
[142] Kodoma H, Ota H. Transfer of PCB to infants from mothers. Arch Environ Health 1980; 35: 95-100.
[143] Abraham K, Papke O, Wahn U, Helge H. POP accumulation in infants during breast-feeding. Organohalogen Compounds 2000; 48: 25-26.

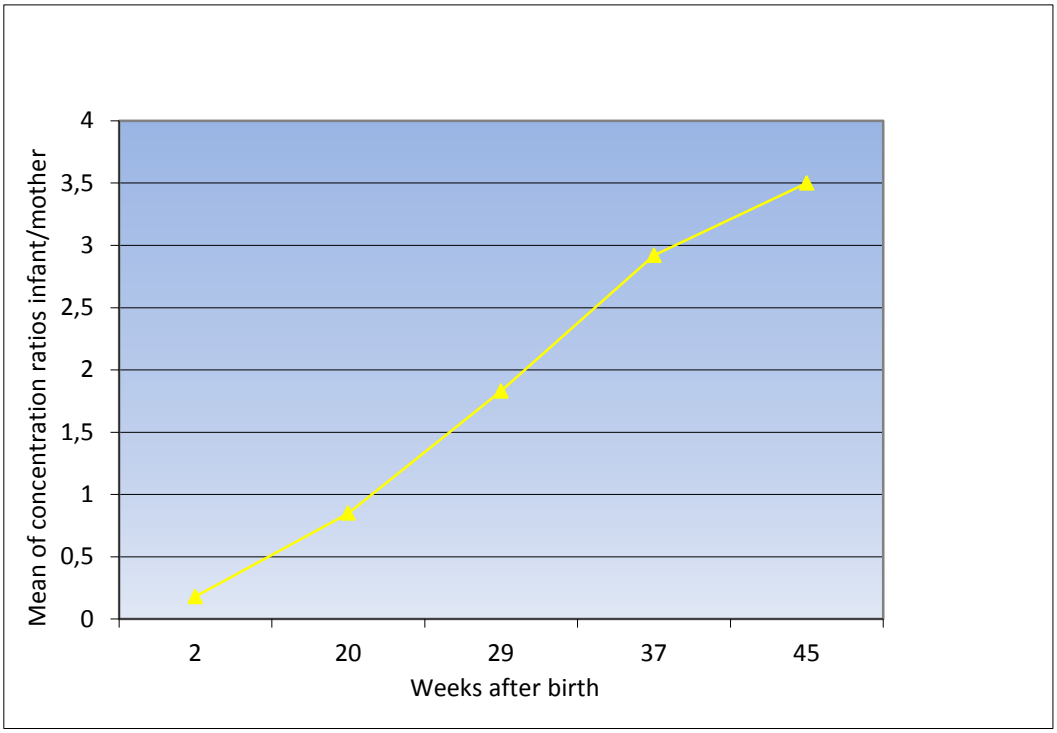

Figure 5.9: Increasing accumulation of PCB in breast-fed infants after birth (Data from Abraham et al. 2000).

6. Health effects of PCB

When the commercial use of PCB began PCB was considered rather harmless with a low acute toxicity but by the time effects were observed in some occupational case studies and later in cohort studies some of which still have follow-up. It was not before the Yusho mass intoxication in 1968 (see later) that PCB mixtures became known as toxic substances, and PCB mixtures became more and more studied in animal experiments. Since then it has been one of the most studied substances.

However, as mentioned above PCB mixtures consist of a large amount of congeners with different health effect properties. About 25 years ago it became possible analytically to separate out most of the congeners. Additionally, some single congeners were synthesized and studied in *in vivo* and *in vitro* experiments, and it became clear that there were two main groups of PCBs in regards to toxicity targets; those with a dioxin-like effect (see earlier) and those without. For both the target organ is the liver though with different receptors.

This means that PCB can have some primary effects but also that levels lower than thresholds in animal experiments can have adverse effects in humans through toxic interactions and enzyme induction and changed metabolism of nutrients, hormones (endocrine disruption), drugs and pollutants. That may be the explanation for the relations in epidemiological studies between PCB exposure of the general population and some civilization diseases such as obesity, diabetes-2, cardiac diseases etc.

Because the chemical exposures of individuals and groups of humans differ and have variations and fluctuations, and the gene expression differs between phenotypes, among which some will be more

susceptible to PCB and the changed metabolism, it will probably be impossible or at least very difficult to make an absolute risk assessment of all human situations.

Indoor exposures, which are mainly due to lower chlorinated congeners, are especially difficult to evaluate, since there is no or very little toxicity data for most of these low-chlorine congeners. The available data is mainly from high-dose animal experiments with PCB mixtures, occupational studies where the high exposures were from PCB mixtures, and finally lower exposure population studies where people mainly have been exposed via food and for the most persistent congeners, and simultaneously have been exposed to other pollutants. In the following selected experimental toxicity data and population studies are discussed.

6.1 Experimental data

Most studies on the effect of PCB on experimental animals have used the various commercial PCB mixtures of hundreds of PCB congeners and sometimes even contaminated by trace impurities of polychlorinated dibenzofurans (PCDFs).

A. Toxicokinetics and metabolism

Many studies confirm that PCB mixtures and individual congeners are readily absorbed (up to 96%) from the gastro-intestinal tract of experimental animals. The absorption depends on the vehicle and the structure of the congeners. The lower chlorinated congeners have a greater absorption. The absorption in experimental animals of PCB in aerosols is comparable to oral exposures, and the dermal absorption is somewhat less efficient (up to 56%) than the other exposure routes. PCBs in dust behave differently, because orally the absorption was only about 60% and dermal higher and about 70%.[144]

Following absorption PCB congeners are bound to lipoproteins in the blood and distributed by the blood to the liver. Initial the highest levels are in the blood, liver and muscle but later PCBs are further redistributed mainly to the kidneys, the skin and adipose fat, but also to the brain.[145] The dioxin-like PCB77 congener was more distributed to the liver and thymus than PCB52.[146]

The metabolism of PCB congeners depends very much on their structure. In general, highly chlorinated PCBs are very resistant to metabolism but the PCBs with less than 3 chlorine atoms are easier metabolized. The metabolism of PCB primary occurs by the hepatic P_{450}-dependent monooxygenase system. Congeners with a pair of un-substituted carbon-atoms in *ortho-meta*-positions are most readily metabolized to various hydroxy-PCBs, because arene oxides are intermediates. A possible reaction chain is simplified in Figure 6.1:

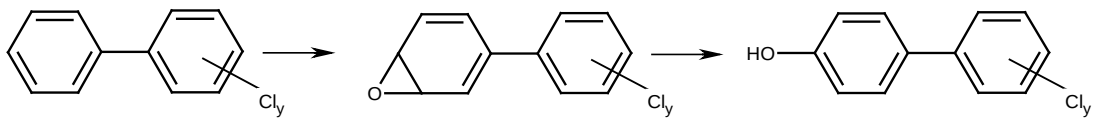

Figure 6.1: Possible metabolism of PCB congeners.

[144] Ertl H, Butte W. Bioaccessibility of pesticides and polychlorinated biphenyls from house dust. J Exp Sci Environ Epidemiol 2012; 22: 574-583.
[145] IPCS Environmental Health Criteria 140 Polychlorinated biphenyls and terphenyls (second edition). Geneva: WHO, 1993
[146] Sargent L, Dragan YP, Erickson C, Laufer CJ, Pitot HC. Study of the separate and combined effects of the non-planar 2, 5, 2′, 5′-and the planar 3, 4, 3′, 4′-tetrachlorobiphenyl in liver and lymphocytes in vivo. Carcinogenesis 1991; 12: 793-800.

For PCB congeners with six or more chlorine atoms and especially without free *ortho-meta*-positions in the benzene rings position, such as for PCB153 and PCB138, the metabolisms are though a different mechanism and are slower. These congeners are retained more in tissues.

Some hydroxylated metabolites of PCBs (OH-PCBs) are also present in human blood, and there is increasing evidence that OH-PCBs are important in accounting for the toxicities associated with PCBs. The five metabolites with the highest concentration in blood are normally 4-OH-PCB187, 4-OH-PCB146, 4-OH-PCB107, 3'-OH-PCB138 and 3-OH-PCB153. The percentage of total OH-PCBs to total PCBs in human blood ranges from 13 to 44%.[147]

Besides hydroxy-metabolites, also sulfur-containing metabolites (methyl sulfones) and de-chlorinated metabolites have been identified.[148]

The minor excretions of PCB congeners are to a large extent also dependent on this metabolism of PCB to more polar compounds. These hydroxy-metabolites are more polar and water-soluble, and they can be excreted as glucuronide conjugates in the bile and feces. The excretion of PCB and metabolites via the urine is insignificant.

At steady state, the mono- and dichlorobiphenyls were eliminated from adipose tissue of mice and rats during a few days but the tetrachlorobiphenyls had a longer half-life of around 15 days, and the higher PCBs had an even longer half-life. For instance, the most slowly metabolized congener PCB153 had a biological half-life of 450 days in rats.[149]

Many animal studies have shown that all PCB congeners can partly cross the placental barrier and accumulate in the tissues of fetuses. In a study with mice exposed to PCB153 3% of the maternal body burden was transferred to the fetuses.[150]

More PCB is transferred to the offspring by lactation. After 5 weeks of suckling the offspring had received 100 fold more PCB than its body burden at birth. In studies with exposed monkeys PCB levels in milk were 20 fold higher than maternal serum levels, and the PCB levels in the blood of the offspring were 2-5 fold higher than the mothers, and intoxication were observed in nursing but not in newborns.[151]

B. Non-cancer endpoints, dose-response, NOAELs

The acute toxicity of commercial mixtures of PCB is rather low, with rat oral LD_{50} ranging from 1-11 g/kg b w and rabbit dermal LD_{50} ranging from 0.8-3.2 g/kg bw. A few single congeners have been tested. Some non-dioxin-like (PCB7, PCB31, PCB52, PCB101, PCB149, PCB153 and PCB183) had oral mice LD_{50}'s of 1-8

[147] Fangstrom B, Athanasiadou M, Grandjean P, Weihe P, Bergman A. Hydroxylated PCB metabolites and PCBs in serum from pregnant Faroese women. Environ Health Perspect 2002; 110: 895-899.
[148] Ahlborg UG, Hanberg A, Kenne K. Risk Assessment of polychlorinated biphenyls (PCBs). Nord 1992:26. Copenhagen: Nordic Council of Ministers, 1992.
[149] IPCS Environmental Health Criteria 140 Polychlorinated biphenyls and terphenyls (second edition). Geneva: WHO, 1993.
[150] Vodicnik MJ, Lech JJ. The transfer of 2,4,5,2',4',5'-hexachlorobiphenyl to fetuses and nursing offspring. Toxicol Appl Pharmacol 1980;54:293-.
[151] Concise International Chemical Assessment Document 55. Polychlorinated biphenyls: human health aspects. Geneva: WHO, 2003. http://www.who.int/ipcs/publications/cicad/en/cicad55.pdf

g/kg bw but the dioxin-like PCB77 and PCB169 were more than 1000 fold more acute toxic with oral guinea pig LD_{50}'s less than 1 mg/kg bw.[152]

The toxic effects commonly observed by repeated administration of PCB mixtures and individual congeners include a wasting syndrome (progressive weight loss), effects on the liver, skin, immune- and reproductive system and endocrine disruption. In 2-years feeding study with rats exposed to various Aroclor mixtures of 1-2 mg/kg bw/day effect such as hepatocellular hypertrophy and vacuolization were observed. Perinatal exposure to purity-controlled single PCB congeners PCB52, PCB138, or PCB180 altered toxicogenomic profiles in peripheral blood of rats after 4 months.[153]

In monkeys exposed to Aroclor 1254 in the feed for 72 months the lowest-observable-adverse-effect-level (LOAEL) was 0.008 mg/kg bw/day for increased liver weight.[154]

Some single PCB congeners have been studied for 13-weeks oral toxicity in rats. The most sensitive organs were the liver and thyroidea. The LOAEL values determined are shown in Table 6.1. The NOAEL values were estimated to be tenfold lower than the LOAELs:[155]

Table 6.1: LOAEL values in rats determined for selected PCB congeners (ATSDR 2000).

PCB congener	LOAEL value mg PCB/kg bw/day
PCB28	0.36
PCB128	0.42
PCB153	0.34
PCB77*	0.087
PCB105*	0.039
PCB118*	0.17
PCB126*	0.0008

*Dioxin-like

Reproductive toxicity

The lowest doses (LOAEL) for which developmental exposures to commercial PCB mixtures have been shown to produce postnatal effects on growth and function in several species, was at 0.25 mg/kg/day for rodents and 0.008 mg/kg/day for nonhuman primates.

High exposures to PCB mixtures with more than 41% chlorine have had effects on the reproduction of various experimental animals. Endpoints affected have been for instance:[156]

- Lower reproductive organ weights in exposed males
- Lower numbers of sperm in exposed males
- Altered estrous/menstrual cycles
- Lower number of exposed females mated

[152] Ahlborg UG, Hanberg A, Kenne K. Risk Assessment of polychlorinated biphenyls (PCBs). Nord 1992:26. Copenhagen: Nordic Council of Ministers, 1992.
[153] De Boever P, Wens B, Boix J, Felipo V, Schoeters G. Perinatal exposure to purity-controlled polychlorinated biphenyl 52, 138, or 180 alters toxicogenomic profiles in peripheral blood of rats after 4 months. Chem Res Toxicol 2013; 26: 1159-67.
[154] Concise International Chemical Assessment Document 55. Polychlorinated biphenyls: human health aspects. Geneva: WHO, 2003. http://www.who.int/ipcs/publications/cicad/en/cicad55.pdf
[155] ATSDR 2000
[156] Golub MS, Donald JM, Reyes JA. Reproductive Toxicity of Commercial PCB Mixtures: LOAELs and NOAELs from Animal Studies. Environ Health Perspect 1991; 94: 245-253.

- Lower maternal weight gain during pregnancy
- Fewer completed pregnancies
- Greater incidence of malformations
- Fewer offspring/litter
- Lower offspring birth weights
- Less postnatal survival of offspring
- Lower postnatal weight gain in offspring
- Lower reproductive organ weights in offspring
- Impaired function in offspring.

Oral exposure of female rats to 1 mg/kg bw of an Aroclor mix from 28 days before breeding and continued until weaning at postnatal day 21 resulted in permanent developmental hearing deficits in the offspring.

Immunotoxicity

The immune system has long been known to be sensitive to PCBs, and it is among the most sensitive of all organ systems.[157] Administration of PCBs to animals causes atrophy of the thymus gland and immunosuppression, and the evidence suggests that much of this action is mediated via activation of the Ah receptor.

A comparative study of mice exposed to eight daily doses of respectively 100 mg PCB52 and 8 mg PCB77/kg bw showed that the dioxin-like PCB77 congener was more distributed to the liver and thymus, and caused thymus atrophy at a lower dose, than that causing liver toxicity. Significantly higher exposure to PCB52 had no effect.[158]

Neurotoxicity

Reactive oxygen species produced by PCBs (Aroclor 1254) may alter blood–brain barrier integrity in rats but natural antioxidant quercetin can modify the effect.[159]

Some lower chlorinated NDL-PCBs, in particularly PCB28 and PCB52, can potentiate the human $GABA_A$ receptor, which may be relevant for neurotoxicity. PCB28 is more potent than PCB52 but there was an additive effect.[160]

Neonatal exposure to PCB28 and PCB52 (10 days of age) altered spontaneous motor activity and for PCB 52 even impaired learning and memory functions in mice.[161] In similar studies the dioxin-like PCB 105 and PCB126 had a neurotoxic effect in the brain and changed the behavior of mice.[162]

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[157] Toxicological profile for polychlorinated biphenyls. Atlanta: ATSDR, November 2000.
[158] Sargent L, Dragan YP, Erickson C, Laufer CJ, Pitot HC. Study of the separate and combined effects of the non-planar 2, 5, 2′, 5′-and the planar 3, 4, 3′, 4′-tetrachlorobiphenyl in liver and lymphocytes in vivo. Carcinogenesis 1991; 12: 793-800.
[159] Selvakumar K, Prabha RL, Saranya K, Bavithra S, Krishnamoorthy G, Arunakaran J. Polychlorinated biphenyls impair blood–brain barrier integrity via disruption of tight junction proteins in cerebrum, cerebellum and hippocampus of female Wistar rats: Neuropotential role of quercetin. Human Exp Toxicol 2013; 32: 706–720.
[160] Fernandes EC, Hendriks HS, van Kleef RG, van den Berg M, Westerink RH. Potentiation of the human GABA(A) receptor as a novel mode of action of lower-chlorinated non-dioxin-like PCBs. Environ Sci Technol 2010; 44: 2864-2869.
[161] Eriksson P, Fredriksson A. Developmental neurotoxicity of four ortho-substituted polychlorinated biphenyls in the neonatal mouse. Environ Toxicol Pharmacol 1996; 1: 155-165.
[162] Eriksson P, Fredriksson A. Neurotoxic effects in adult mice neonatally exposed to 3,3'4,4'5-pentachlorobiphenyl or 2,3,3'4,4'-pentachlorobiphenyl. Changes in brain nicotinic receptors and behaviour. Environ Toxicol Pharmacol 1998; 5: 17-27.

The olfactory system may be a potentially significant portal for the entry of airborne PCBs. In a study ferrets, mammalian carnivores with large olfactory bulbs, were kept in an indoor enclosure, where they were continuously for 5 years exposed to low concentrations of PCB (total PCBs 260 ng/m^3 air) in the ambient air of an animal care room, which had PCB containing sealants. Tetrachlorinated PCBs dominated the congener profile of ambient air, with PCB52 being found at the highest concentration. In contrast, the congener profile in adipose tissue resembled that of most exposed or unexposed animals, with hexa- and hepta-substituted congeners being the major congeners present. The olfactory bulbs in the brain of the exposed animals had the highest total PCB concentration (642 ng/g lipids), while the liver, adipose tissue, and brain had levels of 202, 303, and 170 ng/g lipids, respectively. The data suggested that inhaled PCBs pass into the dentrites of olfactory sensory neurons and are transported via olfactory axons directly to the bulbs where they accumulate.[163] In Figure 6.2a is shown the PCB pattern in the air the ferrets were exposed to:

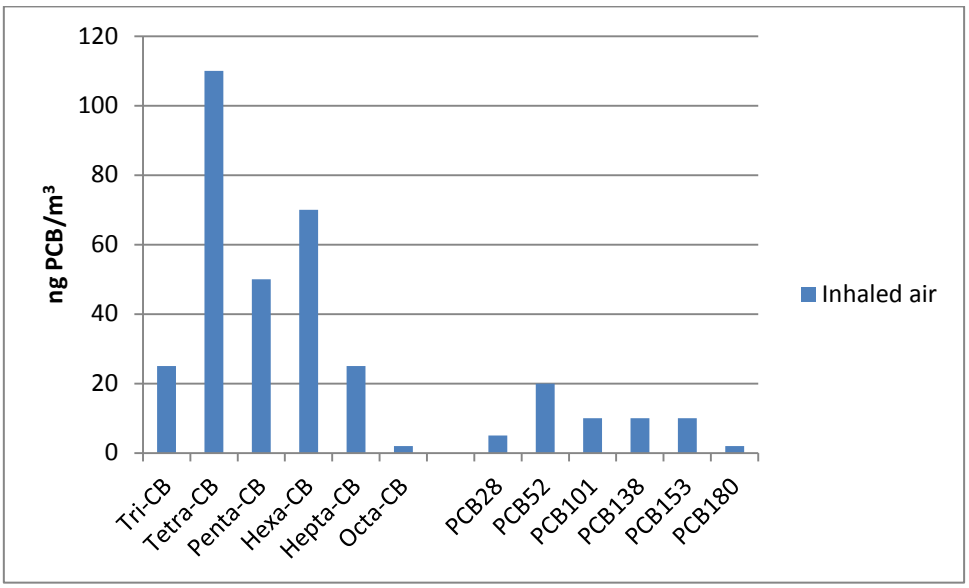

Figure 6.2a: PCB pattern in air the ferrets were exposed to from sealants (based on data from Apfelbach et al. 1998).

In Figure 6.2b the different PCB profiles in olfactory bulbs, brain and adipose tissues are illustrated showing the large selective accumulation of PCB28 and PCB52 in olfactory bulbs:

[163] Apfelbach R, Engelhart A, Behnisch P, Hagenmaier H. The olfactory system as a portal of entry for airborne polychlorinated biphenyls (PCBs) to the brain? Arch Toxicol 1998; 72:314-317.

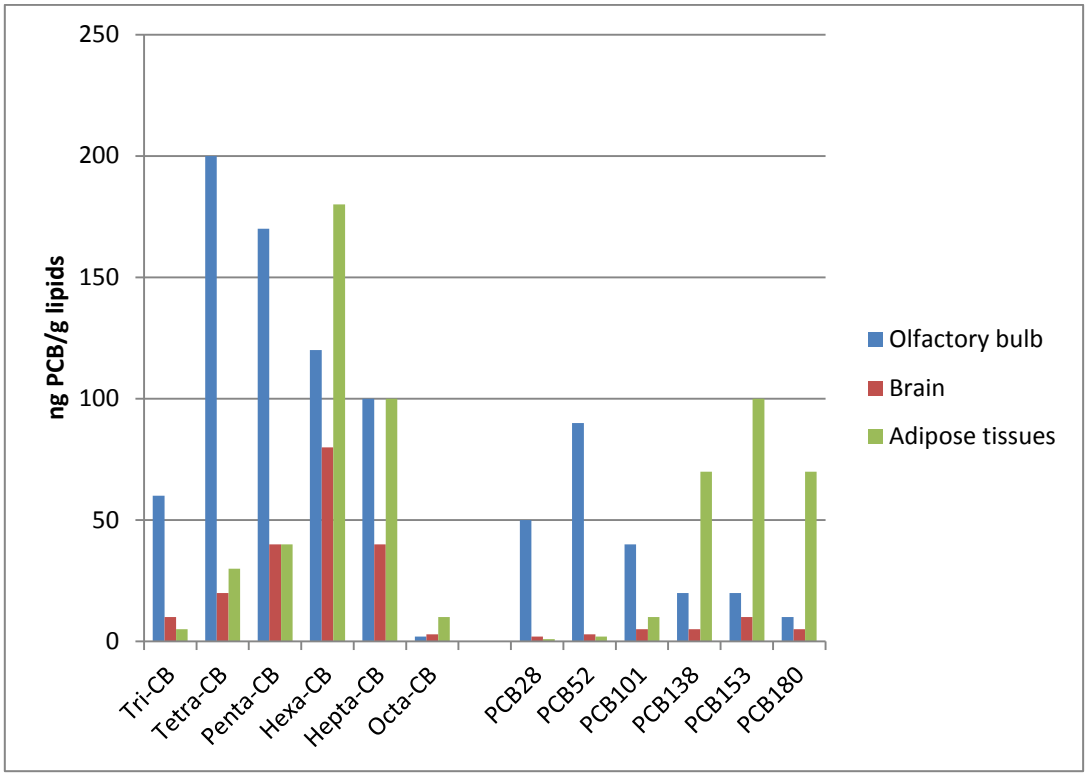

Figure 6.2b: PCB profiles in olfactory bulbs, brain and adipose tissues of ferrets after inhalation exposure to PCB from sealants and at lower levels than the action limit (based on data from Apfelbach et al. 1998).

The *ortho*-substituted congeners alter dopamine metabolism, cause generation of reactive oxygen species by activation of respiratory bursts in neutrophils, trigger contraction of pregnant rat uterus muscle, stimulate insulin release from RIMm5F cells), and kill cerebellar granule cell neurons. Concerning specifically PCB28, PCB47 and PCB52 they incorporate into lipid bilayers and with its bulky, three-dimensional *ortho*-substituted congener structure it disrupts mitochondrial and endoplasmic reticulum membrane function to a greater degree than coplanar congeners.[164]

Cardiovascular effects

The dioxin-like PCB77 stimulates pro-inflammatory pathways in the vascular endothelium in mice and therefore facilitate development of atherosclerosis, which can be prevented by supplement of omega-3 fatty acids.[165]

Also DL-PCB126 exposure in female rats resulted in effects on cardiovascular risk factors, such as increased serum cholesterol, blood pressure, and heart weight. Of these effects of PCB 126, the increase in blood pressure was dependent on estrogen status.[166] PCB180 has a unique porphyrinogenic action in female rats.[167]

[164] Tan Y, Li D, Song R, Lawrence D, Carpenter DO. Ortho-substituted PCBs kill thymocytes. Toxicol Sci 2003; 76: 328-337.
[165] Majkova Z, Layne J, Sunkara M, Morris AJ, Toborek M, Hennig B. Omega-3 fatty acid oxidation products prevent vascular endothelial cell activation by coplanar polychlorinated biphenyls. Toxicol Appl Pharmacol2011; 251: 41-49.
[166] Lind PM, Örberg J, Edlund U-B, Sjöblom L, Lind L. The dioxin-like pollutant PCB 126 (3,3',4,4',5-pentachlorobiphenyl) affects risk factors for cardiovascular disease in female rats. Toxicology Letters 2004; 150: 293–299.
[167] Koss G, Meyer-Rogge D, Seubert S, Seubert A, Losekam M. 2,2',3',4,4'5,5'-Hepatachlorobiphenyl (PCB 180) -- on its toxicokinetics, biotransformation and porphyrinogenic action in female rats. Arch Toxicol 1993; 67: 651-654.

Endocrine effects

The endocrine system is an important target for PCBs. Direct and indirect evidence of weak estrogenic activity was observed for various Aroclors.[168] Several models have shown direct modulation of nuclear steroid hormone-dependent gene expression by PCBs. Furthermore, depending on their structure, monohydroxylated PCB metabolites can act as estrogen agonists or antagonists.

A series of PCB congeners were evaluated for their estrogenic or anti-estrogenic potencies using *in vitro* reporter gene assay. The results suggest that some lower-chlorinated congeners exhibit weakly estrogenic effects, while higher-chlorinated ones are primarily anti-estrogenic.[169]

Polychlorinated biphenyl (PCB) mixtures and congeners effectively reduce circulating concentrations of thyroxin (T_4). This is thought to occur because of their ability to induce the UDP-glucuronosyl transferase that conjugate T_4 and enhance the subsequent excretion of the glucuronide into bile.[170]

After 5 months feeding of 0.09 mg Aroclor/kg bw/day to rats effects were observed on thyroidea with decreased levels of thyroxine (T_4) in blood serum. This may be related to metabolites of PCB, since some hydroxylated metabolites for instance 5-OH-PCB77 bind to transthyretin in plasma of rats and mice, and thereby interfere with the transport of both vitamin A and thyroxine.[171] However, also sulfate metabolites of PCB can displace thyroxine from binding sites on transthyretin (TTR).[172]

In a rat bioassay chronic exposure to PCB118 caused morphological and functional deterioration of the rat thyroid. PCB118 may be a significant risk factor for thyroid diseases.[173]

The lowest dose applied (0.1 mg PCB118/kg bw/day) in a National Toxicology Program (NTP) two years oral exposure study of 2,3',4,4',5-pentachlorobiphenyl (PCB118) with female rats didn't induce cancer but lead to dose dependent changes in enzyme and hormone levels with decrease of serum total thyroxin (T_4) and increase of CYP1A1-associated ethoxyresorufin *O*-deethylase (EROD), CYP1A2-associated acetanilide-4-hydroxylase, and CYP2B-associated pentoxyresorufin *O*-deethylase.[174]

In a study, where mice were fed a *low-fat* diet, PCB-77 was associated with significant impairment of glucose and insulin tolerance, and PCB-126 significantly impaired insulin tolerance, compared with untreated mice fed the same diet.[175] The effects lasted two weeks following cessation of PCB exposure. If the mice received the PCB congeners with a *high-fat* diet, there was no effect of the PCB congeners. The

[168] IPCS Environmental Health Criteria 140 Polychlorinated biphenyls and terphenyls (second edition). Geneva: WHO, 1993.
[169] Pliskova M, Vondracek J, Canton RF, Nera J, Kocan A, Petrík J, Trnovec T, Sanderson T, van den Berg M, Machala M. Impact of polychlorinated biphenyls contamination on estrogenic activity in human male serum. Environ Health Perspect 2005; 113: 1277-1284.
[170] Martin LA. Differential effects of polychlorinated biphenyl (PCB) mixtures and congeners on the disposition of thyroxine (T4). Toxicol.Sci 2002; 60: Abstract 1314.
[171] Brouwer A, van den Berg KJ. Binding of a metabolite of 3,4,3',4'-tetrachlorobiphenyl to transthyretin reduces serum vitamin A transport by inhibiting the formation of the protein complex carrying both retinol and thyroxin. Toxicol Appl Pharmacol 1986; 85: 301-312.
[172] Grimm FA, Lehmler HJ, He X, Robertson LW, Duffel MW. Sulfated metabolites of polychlorinated biphenyls are high-affinity ligands for the thyroid hormone transport protein transthyretin. Environ Health Perspect 2013; 121: 657–662.
[173] Tang JM, Li W, Xie YC, Guo HW, Cheng P, Chen HH, Zheng XQ, Jiang L, Cui D, Liu Y, Ding GX, Duan Y. Morphological and functional deterioration of the rat thyroid following chronic exposure to low-dose PCB118. Exp Toxicol Pathol 2013; 265: 989-994.
[174] NTP toxicology and carcinogenesis studies of 2,3',4,4',5-pentachlorobiphenyl (PCB 118) (CAS No. 31508-00-6) in female Harlan Sprague-Dawley rats (Gavage Studies). National Toxicology Program Technical Report Series 2010; 559: 1-183.
[175] Baker NA, Karounos M, English V, Fang J, Wei Y, Stromberg A, Sunkara M, Morris AJ, Swanson HI, Cassis LA. Coplanar polychlorinated biphenyls impair glucose homeostasis in lean C57BL/6 mice and mitigate beneficial effects of weight loss on glucose homeostasis in obese mice. Environ Health Perspect 2013; 121: 105–110.

researchers concluded that the aryl hydrocarbon receptor played a key role in the effect on glucose homeostasis.

A new study showed that chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-induced insulin resistance and hyperinsulinemia in both lean and diet-induced obese mice and exacerbated whole-body insulin resistance in obese mice.[176]

A quite new study find that low-level PCB exposure change bird songs by mimic hormones and interfere with development of the part of the bird's brain that governs song and song structure.[177]

C. Cancer endpoints

In general, PCB mixtures or congeners seem not to be genotoxic in available test systems, however, the lower chlorinated mixture Aroclor 1221 and the single congener 4-chlorobiphenyl (PCB3) were mutagenic in the Ames *in vitro* test with *Salmonella typhimurium* and metabolic activation.[178] PCB3 also induces mutations in the livers of transgenic rats.[179] The active substance was probably the 4-hydroxy-metabolite of PCB3.[180] High-chlorinated PCB mixtures are routinely used in the Ames test and other test systems to activate liver enzymes preparations added for metabolism of the test substance. Thus, highly chlorinated PCB may convert non-genotoxic xenobiotics into genotoxic metabolites.

A large 2-years rat study of four PCB mixtures (Aroclors 1016, 1242, 1254 and 1260) in doses from 25-200 ppm in the feed was reported in 1996. Female rats experienced statistical significant increased incidences of liver tumors for all tested with Aroclors. Aroclor 1254 was the most potent carcinogen. In male rats only Aroclor 1260 induced tumors. The numbers of malignant tumors increased with dose.[181]

Only a few single congeners have been tested in long-term bioassays. In a NTP study, oral administration of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) resulted in significantly increased incidence of hepatocellular adenomas, cholangiocarcinomas, lung cystic keratinizing epitheliomas, and oral mucosa (gingiva) squamous-cell carcinomas in female rats.[182]

In another more recent NTP study demonstrated that there was clear evidence of carcinogenic activity of 2,3',4,4',5-pentachlorobiphenyl (PCB118), after two years of oral exposure to 4.6 mg PCB118/kg bw/day causing cancer of the liver, lung, and uterus and possibly of the pancreas plus a variety of other toxic effects at several sites of female rats.[183]

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[176] Grey SL, Shaw AC, Gagne AX, Chan HM. Chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-Induced insulin resistance and hyperinsulinemia in mice. J Toxicol Environ Health A. 2013; 76: 701-715.
[177] DeLeon S, Halitschke R, Hames RS, Kessler A, Timothy J. DeVoogd, Dhondt AA. The Effect of Polychlorinated Biphenyls on the Song of Two Passerine Species. PLOS One. Sep 18, 2013. DOI: 10.1371/journal.pone.0073471.
[178] Wyndham C, Devenish J, Safe S. The in vitro metabolism, macromolecular binding and bacterial mutagenicity of 4-chlorobiphenyl, a model PCB substrate. Res Commun Chem Pathol Pharmacol 1976; 15: 563-570.
[179] Lehmann L, Esch HL, Kirby PA, Robertson LW, Ludewig G. 4-Monochlorobiphenyl (PCB 3) induces mutations in the livers of transgenic Fisher 344 rats. Carcinogenesis 2007; 28: 471–478.
[180] Ludewig G, Lehmann L, Esch H, Robertson LW. Metabolic activation of PCBs to carcinogens in vivo - a review. Environ Toxicol Pharmacol 2008; 25: 241-246.
[181] Cogliano VJ. Assessing the cancer risk from environmental PCBs. Environ Health Perspect 1998; 106: 317–323.
[182] NTP toxicology and carcinogenesis studies of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) (CAS No.57465–28–8) in female Harlan Sprague-Dawley rats (Gavage Studies). National Toxicology Program Technical Report Series 2006, 520: 4–246.
[183] NTP toxicology and carcinogenesis studies of 2,3',4,4',5-pentachlorobiphenyl (PCB 118) (CAS No. 31508-00-6) in female Harlan Sprague-Dawley rats (Gavage Studies). National Toxicology Program Technical Report Series 2010; 559: 1-183.

PCB126 and PCB153 were promoters of liver tumors in mice initiated by diethyl nitrosamine. A small additive effect by the two congeners was observed.[184] Synergistic interactions for such tumor promotion have been observed for combinations of PCB 77 and PCB 52 in rat liver.[185] In another study the three congeners PCB126, PCB105 and PCB153 were all tumor promoters, the first one was far more potent.[186] In another study PCB3, PCB15, PCB52 and PCB77 were promoters of liver cancer but not PCB12 and PCB38. PCB3 and PCB15 were also liver cancer initiators.[187]

D. Toxicological mechanisms

PCBs main toxicological mechanism is through induction of hepatic microsomal cytochrome P_{450} mono-oxygenases. This induction may generate reactive biological intermediates and interfere (potentiate or antagonize) with the actions of biological essential chemicals and xenobiotics. PCB mixtures induce 4 types of cytochrome P_{450} (CYP). CYP1A1 and CYP1A2 are of the 3-methylcholanthrene (aryl hydrocarbon) type, and CYP2B1 and CYP2B2 are of the phenobarbital type. The dioxin-like congeners are interacting with the CYP1A1 and CYP1A2 with binding to the aryl hydrocarbon receptor (AhR).

The aryl hydrocarbon receptor (AhR) regulates and can for example modulate melanogenesis in humans, which lends mechanistic plausibility of a role of PCBs in melanoma and development of dark skin of PCB intoxicated infants.[188] The dioxin-like PCB126 is a potent AhR agonist, and it induced hepatotoxicity in rats, which could be modulated by dietary selenium.[189]

PCBs also interact with the constitutive androstane and pregnane xenobiotic receptor (CAR/PXR) inducing the expression of catabolic cytochrome P450 enzymes of the CYP1A and CYP3A families. Certain highly chlorinated NDL-PCBs are potent activators of rodent PXR but antagonize its human ortholog, the steroid and xenobiotic receptor (SXR), inhibiting target gene induction. Thus, exposure to PCBs may dull the human xenobiotic response, inhibiting the detoxification of steroids, bioactive dietary compounds, and xenobiotics normally mediated by SXR. The antagonistic PCBs (specifically PCB 184 and PCB 197 but also PCB153) are among the most stable and abundant PCBs in human tissues. These findings have important implications for understanding the biologic effects of PCB exposure and the use of animal models to predict the potential human risk. Humans may, like monkeys, guinea pigs and minks, be more sensitive to PCB toxicity than rodents.[190]

Developmental neurotoxicity has emerged as a particularly vulnerable endpoint in chronic low-level PCB toxicity. This effect could be mediated by non-dioxin-like PCB's ability to alter the spatial and temporal fidelity of Ca^{2+}-signals. The molecular and cellular mechanism is through the structure and function of

[184] Rignall B, Grote K, Gavrilov A, Weimer M, Kopp-Schneider A, Krause E, Appel KE, Buchmann A, Robertson LW, Lehmler HJ, Kania-Korwel I, Chahoud I, Schwarz M. Biological and tumor-promoting effects of dioxin-like and non-dioxin-like polychlorinated biphenyls in mouse liver after single or combined treatment. Toxicol Sci 2013; 133: 29-41.
[185] Sargent LM, Sattler GL, Roloff B, Xu Y, Sattler CA, Meisner L, Pitot HC. Ploidy and specific karyotypic changes during promotion with phenobarbital, 2, 5, 2', 5'-tetrachlorobiphenyl, and/or 3, 4, 3', 4'-tetrachlorobiphenyl in rat liver. Cancer Res 1992; 52: 955-962
[186] Hemming H, Flodström S, Wärngård L, Bergman Å, Kronevi T, Nordgren I, Ahlborg UG. Relative tumour promoting activity of three polychlorinated biphenyls in rat liver. Eur J Pharmacol1993; 248:163-174.
[187] Espandiari P, Glauert HP, Lehmler HJ, Lee EY, Srinivasan C, Robertson LW. Polychlorinated biphenyls as initiators in liver carcinogenesis: resistant hepatocyte model. Toxicol Appl Pharmacol 2003; 186: 55–62.
[188] Luecke S, Backlund M, Jux B, Esser C, Krutmann J, Rannug A. The aryl hydrocarbon receptor (AHR), a novel regulator of human melanogenesis. Pigment Cell Melanoma Res 2010; 23: 828–33.
[189] Lai IK, Chai Y, Simmons D, Watson WH, Tan R, Haschek WM, Wang K, Wang B, Ludewig G, Robertson LW. Dietary selenium as a modulator of PCB 126-induced hepatotoxicity in male Sprague-Dawley rats. Toxicol Sci 2011; 124: 202-214.
[190] Tabb MM, Kholodovych V, Grün F, Zhou C, Welsh WJ, Blumberg B. Highly Chlorinated PCBs Inhibit the Human Xenobiotic Response Mediated by the Steroid and Xenobiotic Receptor (SXR). Environ Health Perspect 2004; 112: 163–169.

ryanodine receptors (RyRs) in muscle and nerve cells. Experiments with rats confirmed that developmental exposure via the maternal diet to NDL PCB95 (2,2',3,5'6-pentachlorobiphenyl), a potent RyR potentiator, phenocopies the dendrite-promoting effects of Aroclor 1254. This effect was not seen by PCB66 (2,3,4',4-tetrachlorobiphenyl).[191]

It has been shown that PCB138, PCB153, and PCB180 induce changes in the gut microbiome of mice with little exercise but not in mice exercising in a running wheel. This indicates some interactions between exercise and PCB.[192]

6.2 Epidemiological and Clinical studies

A. Accidental exposures

Yusho

"Yusho", which means "oil disease" in Japanese, was a mass food poisoning involving more than 1800 people, which was discovered in Western Japan (Fukuoka Prefecture) in October 1968.[193] The poisoning was caused by daily ingestion during approximately half a year of a commercial brand of rice cooking oil incidentally contaminated by large amount of PCB and traces of polychlorinated quaterphenyls (PCQs) more toxic transformation products such as polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-*p*-dioxins (PCDDs).

The contamination happened because of a leak in a heat-transfer installation for deodorizing the oil. The heat-transfer liquid contained Kanechlor 400, a commercial PCB mixture with 48% chlorine. The contaminated oil contained about 1000 ppm of PCBs and PCQs, and 5 ppm of PCDFs. This concentration of PCDFs was 250 folds higher than in the Kanechlor product, because it had been heated.

The disease was characterized by severe acne-like eruptions of the skin especially in the face. Other major signs or symptoms were:

- Dark-brown pigmentation of skin, nails, lips, and gingival and buccal mucosa
- Distinctive hair follicles
- Itching
- Increased sweating at the palms
- Swelling of the upper eyelids and increased eye discharge
- Hyperemia of the conjunctiva ("red eyes")

At the outbreak in 1968 the PCB levels in adipose tissue from the patients were 13-76 ppm, and the PCDF levels were 9.3 ppb in adipose and 17.6 ppb in the liver. 10-15 years after the poisoning PCB in the blood was 3-6 ppb in Yusho victims, which were 2-4 folds higher than controls. PCQ was about 2 ppb in the blood, which was 100 fold more than in controls.

[191] Wayman GA , Yang D, Bose DD, Lesiak A, Ledoux V, Bruun D, Pessah IN, Lein PJ. PCB-95 promotes dendritic growth via ryanodine receptor-dependent mechanisms. Environ Health Perspect 2012; 120: 997-1002.
[192] Choi JJ, Eum SY, Rampersaud E, Daunert S, Abreu MT, Toborek M. Exercise attenuates PCB-induced changes in the mouse gut microbiome. Environ Health Perspect 2013; 121:725–730.
[193] Kuratsune M. Yusho, with reference to Yu-Cheng. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.

A study from 1987 showed a small increased risk for cancer in Yusho victims. Since Yusho exposure included PCQ and 250 fold more PCDFs than at normal PCB exposure the health outcomes cannot directly be used in PCB risk assessment.

YuCheng

In May 1979, eleven years after the outbreak of Yusho in Japan a similar mass poisoning called YuCheng ("oil disease" in Chinese) happened in central Taiwan, where more than 2000 people were poisoned by ingestion rice bran oil contaminated with PCB and got characteristic symptoms, such as chloracne, hyperpigmentation, dilation and hyper secretion of conjunctival glands.[194] Some newborns of exposed mothers had a dark skin and were called "cola-colored babies". The contamination was caused by a leak in a similar heat-transfer system for deodorizing of rice oils as in Japan. The PCB mixture used in the system was, however, the more chlorinated Kanechlor 500. The levels of PCB (30-400 ppm) in the contaminated oils were much lower (3-30 fold, in average 10 fold) than in Japan. The contents of PCDFs were as in Japan about 0.2% of the PCB content.

In 1968, when Yusho happened, it was not possible to analyze blood samples. It was different in Taiwan, where in 1979 the blood levels measured in 1246 victims had mean and median levels around 60 ppb with 10 fold higher max values. Levels in adipose tissues were about 10 ppm PCB on lipid basis.

A cohort of 1837 YuCheng exposed people was followed through December 31, 1991. The mortality of chronic liver disease and cirrhosis 13 years after the outbreak was almost 3 fold higher than expected.[195]

In 1985 a field survey was initiated of 118 living children, who had been born between June 1978 and March 1985 to mothers poisoned by PCBs and their derivatives in the 1978-1979 incidents and a matched control group. Various test methods were used to assess the cognitive development of these children. The result was that the exposed YuCheng children had poorer cognitive development.[196] A 24-year follow-up study of a YuCheng cohort of 1054 victims showed that the risk of diabetes among women - but not men - was doubled. Women diagnosed with chloracne had even more than 5 fold higher risk for diabetes and more than 3 fold risk of hypertension compared to the chloracne free victims.[197]

Food contamination in Belgium

During the years many incidences have happened around the world with extreme food contamination by PCB. In February 1999 a contamination incident occurred on several farms in Belgium. The use of 60 tons PCB contaminated fat from a fat rendering company for production of approximately 500 tons of animal feed resulted in the introduction of approximately 50 kg PCB and 1 gram of PCDFs in the commercial food chain.[198] The incident was discovered first in Belgian chicken farms because of a decrease in egg production

[194] Rogan WJ. Yu-Cheng. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.
[195] Yu ML, Guo YL, Hsu CC, Rogan WJ. Increased mortality from chronic liver disease and cirrhosis 13 years after the Taiwan "yucheng" ("oil disease") incident. Am J Ind Med 1997; 31: 172-175.
[196] Lai TJ, Guo YL, Guo NW, Hsu CC. Effect of prenatal exposure to polychlorinated biphenyls on cognitive development in children: a longitudinal study in Taiwan. British J Psychiatry 2001; 178: 49-52.
[197] Wang SL, Tsai PC, Yang CY, Guo YL. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care 2008; 31: 1574–1579.
[198] Covaci A, Ryan JJ, Schepens P. Patterns of PCBs and PCDD/PCDFs in chicken and pork fat following a Belgian food contamination incident. Chemosphere 2002; 47: 2007-217.

and hatching, and an epidemic of “chicken edema disease”, which previously have been seen other places in bird poisoning by chlorinated chemicals.[199]

B. Occupational exposures

A recent large Danish assessment with many details has been published by the Work Environment Research Council.[200] In addition a recent Nordic document has been published.[201]

From previous production of PCB and PCB containing materials and articles

The exposure of workers to PCB was already studied in the 1930s in industries producing PCB and dielectric oils for transformers and capacitors, and various effects were reported, such as chloracne, digestive disturbances and impotence. Sometimes the PCB exposures could be massive and mixed with polychlorinated naphthalenes (PCN) and polychlorinated terphenyls (PCT). In the 1950s in the USA the average concentrations of PCB in workroom air from several plants at capacitor impregnating ranged 0.1 to 5.8 mg/m^3 with a maximum of 10 mg/m^3 which the workers found unbearable irritating. In an Italian capacitor-producing plant where worker got chloracne the levels in the 1950s were 5-7 mg/m^3. In the 1960s high occupational levels of PCB were reported from Japan where blood serum levels up to 700 ppb PCB were measured.[202]

Some experts consider Inhalation exposure a major route of occupational exposure to PCBs, and it has been estimated that in capacitor workers a maximum of 80% of the adipose PCBs may have been absorbed by inhalation exposure;[203] however, others concluded that skin contact was more important than inhalation.[204]

Epidemiological studies

A classic study of cancer mortality included 138 905 electric utility workers employed for at least 6 months between 1950 and 1986 at five electrical power plant companies in the USA. The PCB skin and inhalation exposures were estimated by a panel of experts. The total cancer mortality was not elevated but mortality of melanoma and brain cancer increased with cumulated PCB exposure.[205]

A recent study included a ten-year update from 1998 to 2008 of assessing the mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) at three electrical capacitor manufacturing plants.[206] Previous findings, included associations between estimated cumulative PCB exposure and stomach, uterine, and prostate cancer and myeloma mortality were confirmed. Mortality was elevated for some outcomes among subgroups of long-term workers: all cancer, intestinal cancer; amyotrophic lateral sclerosis (women); melanoma (men); melanoma and brain and nervous system cancer (Indiana plant); and

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[199] Gilbertson M. Effects on fish and wildlife populations. In: Kimbrough and Jensen (eds). Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.

[200] Pedersen EB, Jacobsen P, Jensen AA, Brauer C,Gunnarsen L,. Meyer HW, Ebbehøj NE, Bonde JP. Risk of disease following occupational exposure to Polychlorinated Biphenyls. Bispebjerg Hospital, September 2012.
http://www.ask.dk/~/media/ASK/pdf/Rapporter/Udredningsrapport%20om%20PCB%2024juni2013%20pdf.ashx

[201] Lindell B. Polychlorinated Biphenyls (PCBs). Arbete och Hälsa 2012; 46: 1-181.

[202] Criteria for a recommended standard: Occupational exposure to polychlorinated biphenyls (PCBs). Cincinnati: NIOSH, 1977.

[203] Wolff MS. Occupational exposure to polychlorinated biphenyls (PCBs). Environ Health Perspect 1985; 60: 133–138.

[204] Lees PSJ, Corn M, Breysse PN. Evidence of dermal absorption as the major route of body entry during exposure of transformer maintenance and repairmen to PCBs. Ann Ind Hyg Assoc 1987; 48: 257-264.

[205] Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Environ Med 1997; 54: 720-728.

[206] Ruder AV, Hein MJ, Hopf NB, Waters MA. Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: A ten-year update. Int J Hyg Environ Health 2013 Apr 39/j.ijheh.2013.04.006 [Epub ahead of print].

melanoma and multiple myeloma (New York plant). Standardized rates of stomach and uterine cancer and multiple myeloma mortality increased with estimated cumulative PCB exposure. Poisson regression modeling showed significant associations with estimated cumulative PCB exposure for prostate and stomach cancer mortality.

An update of an earlier mortality study of workers exposed to polychlorinated biphenyls (PCBs) in two Italian capacitor manufacturing plants showed possibly increased cancer risks in PCB-exposed workers, affecting, in particular, the digestive system, brain and lymphohemopoietic tissue. However, the limited sample size, the lack of clear trends with duration of employment or with latency period, precluded to derive definite conclusions about PCB exposure and the increased cancer risks.[207]

Present occupational exposures

Workers exposure to PCB has changed in the last 50 years. After banning of closed uses in new equipment, some service and repair workers could still have a considerable exposure, and other workers might have contracted lower exposures to PCB emitted from electric equipment during operation and service and from skin contact to contaminated internal surfaces, furniture and tools that were insufficiently cleaned. A special wide-spread exposure came from leaked ballasts in fluorescent tube lighting used in workshops, garages, offices, schools and other institutions. All these exposures were to the commercial PCB mixtures, and the analytical quantification assessment methods were based on a comparison of a few large peaks in the sample and in the standard mixture.

Nowadays, the major occupational exposures may be:

- In the indoor office and institution environment,
- in the building and construction sector at demolition and especially at PCB renovation,
- for workers who repair, maintain, or remove capacitors and transformers containing PCBs,
- at waste management (collection handling, transport, disposal, recycling, destruction), and
- at accidents and fire-fighting.

Occupational exposure in the indoor environment

Many occupations that work indoors may be exposed to PCB from the building materials. For example, people may work in offices, laboratories, daycare homes, schools, and universities. In a study of a PCB contaminated office building in Achen, Germany, the median and 95 percentile indoor air concentration were 1280 ng PCB/m^3 and 3400 ng PCB/m^3, respectively (see Table 6.2):

Table 6.2: PCB in indoor air of contaminated office building (Broding *et al.* 2007).

ng/m^3	PCB28	PCB52	PCB101	PCB138	PCB153	PCB180	Sum
Median	110	125	11	<2	<2	<2	1280
95 percentile	285	304	45	15	10	4.4	3400

It is clear that airborne PCB mainly consists of the lower chlorinated congeners, and 583 persons who had worked for average 15 years in the building had five folds more of PCB28 and PCB52 in their blood but had the same concentration of the other 4 congeners analyzed in the blood as compared to 205 people in a building without PCB. The half-lives in the blood of PCB28 and PCB52 were determined to respectively 2.2

[207] Pesatori AC, Grillo P, Consonni D, Caironi M, Sampietro G, Olivari L, Ghisleni S, Bertazzi PA. Update of the mortality study of workers exposed to polychlorinated biphenyls (PCBs) in two Italian capacitor manufacturing plants. Med Lav 2013; 104: 107-114.

and 4 years.[208] Exposed people in the contaminated office building had more subjective health complaints (exhaustion and stomach, limb and cardiac complaints) than a control group but there was no correlation between symptoms/complaints and the blood concentration of low-chlorinated PCB congeners. However, an association couldn't be ruled out.[209] The levels of the low-chlorinated PCBs were very low especially for PCB52 indicating some analytical problems. The low levels also made the results uncertain and unreliable. May be it had been better to use the accumulated PCB doses as the exposure measure instead of actual blood levels?

Another German cross sectional study of 30 teachers and employees exposed to indoor air contaminated with PCBs from elastic sealants in a school building were compared to 30 non-exposed controls matched for education and age. Analyses of PCBs in the air and in the elastic sealants were carried out, and blood samples were drawn from the participants in order to estimate exposure levels. The sealant materials contained up to 50 % of PCB. The total concentration of PCB in air ranged from 2.870 to 17.460 ng/m^3. Subjective complaints, learning and memory, executive function, and visual-spatial function were assessed by standardized neuropsychological testing. An objectively exposed subgroup n = 16; with PCB 28 = 0.20 µg/L was identified and compared with 16 paired controls. The mean total PCB concentration in plasma was 4.45 µg/L. The mean plasma level of PCB 28 was 0.28 µg/L and of PCB 101 0.07 µg/L. No neuropsychological effects were demonstrated by traditional significance testing. The objectively exposed subgroup showed a trend towards increased subjective attentional and emotional complaints and attenuated attentional performance. The authors conclude that: "Chronic inhalation of low chlorinated PCBs that involved elevated blood levels was associated with a subtle attenuation of emotional well-being and attentional function".[210] This investigation, which was based on a previous exposure study by Gabrio *et al.* (2000) discussed in Chapter 5.5, lacks the concentration of PCB52 in the blood, although it is the most abundant congener in the indoor air. Therefore, the results and conclusions have to be confirmed. The investigated groups were also very small.

Demolition/renovation of PCB in buildings

The indoor exposures are not directly linked to the commercial mixtures but to the most volatile PCB congeners. At building demolition/renovations exposures will be more related to caulk and dusts than to vapors and the lighter congeners are diminished, and the higher chlorinated congeners dominate. When sealant/caulk is physical removed, skin exposure may also be possible. Nowadays, workers have to be well-protected like workers removing asbestos from buildings. The same may be the case at handling scrapped thermo-windows with PCB.

In a study ten years ago from the greater Boston area in the USA six construction workers were exposed to PCB from caulk containing 70 to 36,200 ppm PCB as Aroclor 1260.[211] The serum-PCB (sum of 57 congeners) was between 1.05 and 8.70 ng/g in the workers and between 1.14 and 1.64 ng/g serum in a reference population. Serum concentrations for the referents and construction workers were highest for congeners

[208] Broding HC, Schettgen T, Göen T, Angerer J, Drexler H. Development and verification of a toxicokinetic model of polychlorinated biphenyl elimination in persons working in a contaminated building. Chemosphere 2007; 68: 1427-1434.
[209] Broding HC, Schettgen T, Hillert A, Angerer J, Göen T, Drexler H. Subjective complaints in persons under chronic low-dose exposure to lower polychlorinated biphenyls (PCBs). Int J Environ Health 2008; 211: 648-657.
[210] Peper M, Klett M, Morgenstern R. Neuropsychological effects of chronic low-dose exposure to polychlorinated biphenyls (PCBs): a cross-sectional study. Environ Health 2005; 4: 22. Page 1-15.
[211] Herrick RF, Meeker JD, Hauser R, Altshul L, Weymouth GA. Serum PCB levels and congener profiles among US construction workers. Environmental Health 2007; 6:25. http://www.ehjournal.net/content/6/1/25

PCB153, PCB138, PCB180, PCB118, and PCB170. The mean level of the lighter PCB congeners in workers was 0.23 ng/g serum, compared to 0.09 ng/g for the reference population. This may indicate that indoor air may contribute to the exposure.

Removal of elastic "Thiokol" sealants from buildings in Finland exposed the workers for about 3100 ng PCB/m^3. The average concentration of PCB in the blood of 22 exposed workers was 3.9 µg/L, while controls had a PCB concentration of 1.7 µg/L blood. For PCB28 and PCB52 there was a correlation between air and blood levels in exposed workers.[212]

In Sweden scientists found that, if the organization of the work was inadequate, removal of elastic PCB sealant material at renovation of buildings could generate extremely high levels of PCB (280-370 µg PCB/m^3) in the workplace air, and examples of effects on the function of the thyroidal gland were also reported.[213]

The same research group observed later that the PCB concentration in the blood of 36 exposed renovation workers exposed to PCB in 2002 were approximately twice the concentration in 33 non-exposed, respectively a geometric mean of 575 ng PCB/g lipid and 267 ng PCB/g lipid determined as the sum of 19 PCB congeners. Samplings 10 month later gave about the same results showing effective protective measures. The result was that PCB56/60 and PCB66 were clearly elevated in presently exposed workers. Other congeners measured, for example PCB28, PCB44, PCB52, PCB70 and PCB110, were indicators of recent workplace exposure, and PCB153 and PCB180 reflected the background exposure from the food intake.[214]

In a later study the research group re-calculated their data and used a geometric means of 580 vs. 260 ng PCB_{19}/g lipid. They included results of blood test for thyroid function and cytokines but neither was associated with PCB exposure.[215]

Waste management

The PCB waste management area is very complex and different globally. In the developing countries only the closed applications have been important, and now when these applications have to be phased-out most countries have no infrastructure to cope with identification, collection and disposal/destruction. Workers exposure may take place all these processes including at destruction in chemical waste incinerators. The PCB Elimination Network (PEN) was established in 2009 by UNEP to assist and train these countries.

Because it is impossible with the bare eyes to see the difference between pure mineral oils, vegetable oils, animal fats and reclaimed PCB-containing oils and lubricants, unintended occupational PCB exposure may happen in this way. Occasionally, waste oils with PCB and chlorinated dibenzofurans have ended up in animal feed stuff and afterwards in foods (and human beings) causing food scandals (see above).

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[212] Kontsas H, Pekari K, Riala R, Bäck B, Rantio T, Priha E. Worker exposure to polychlorinated biphenyls in elastic polysulphide sealant renovation. Ann Occup Hyg 2004; 48: 51-55.

[213] Selden A, Wingfors A, Fedeli C, Johansson N. PCB-belastning och effecter på sköldkörtelfunktionen hos bygnadsarbetare vid sanering av PCB-haltiga fogmassor. Yrkesmedicin YM 3/05. Universitssjukehuset örebro.

[214] Wingfors H, Selden AI, Nilsson C, Haglund P. Identification of markers for PCB exposure in plasma from Swedish construction workers removing old elastic sealants. Ann Occup Hyg 2006; 50: 65-73.

[215] Seldén AI, Lundholm C, Johansson N, Wingfors H. Polychlorinated biphenyls (PCB), thyroid hormones and cytokines in construction workers removing old elastic sealants. Int Arch Occup Environ Health 2008; 82: 99-106.

Building fires

The presence of PCB containing capacitors, transformers and building materials has importance in building fires, where PCB will be released and partly be transformed into the more toxic dioxin-like chlorinated dibenzofurans. The most well-known early transformer-building fire happened on February 5th 1981 in a public office building in Binghamton, New York. Until 1987 there were at least 30 known incidences where large capacitors or transformers have ruptured as a result of fire, explosion or overheating.[216] The number of such incidences since that time has probably accelerated and not necessarily been reported in the scientific literature. At such incidences fire-fighters may be heavily exposed, and their exposures to PCB during fires have been measured to between 3 and 56 µg PCB/m^3 and 12-148 ng dioxin equivalents/m^3.[217]

C. Studies of the general human population

Chronic low-level polychlorinated biphenyl (PCB) exposures remain a significant public health concern since results from epidemiological studies indicate that PCB burden is associated with immune system dysfunction, cardiovascular disease, and impairment of the developing nervous system to name a few.

A general problem with studies of the general population is that the PCB levels here are rather small, and PCB is not acting alone but together with many other xenobiotics so interactions are likely, and it is difficult to establish a definite cause-effect relation.

Effects on male reproduction

Several studies have shown that PCB may interfere with the adult reproductive system. Almost 30 years ago 170 semen samples from New York were analyzed congener-specific for 74 individual PCBs. The mean of PCB_{total} was 5.8 ppb (µg/kg). It was found that for samples with low sperm count, there was a decrease in sperm motility with increasing concentrations of PCBs as PCB153, PCB138 and PCB118.[218]

In the EU INUENDO project (2002-2005) fertility and markers of male reproductive function in Inuit and European populations were investigated in relation to exposure to POP chemicals.[219] In this study PCB153 was used as a marker for PCB in blood. Progressive sperm motility decreased with increasing PCB blood level in all four regions (Sweden, Poland, Ukraine and Greenland) studied and was most evident among the highly exposed Inuit's. However, there were no effects on fertility and sperm count. In the European regions an association between PCB and sperm chromatin integrity in adult males was observed.[220]

In 14-year-old boys prenatally exposed to polychlorinated biphenyls higher PCB exposure was associated with lower serum concentrations of both luteinizing hormone (LH) and testosterone. In addition, sex hormone binding globulin (SHBG) was positively associated with both prenatal and concurrent PCB exposures. Further, prenatal exposure to PCB and DDE showed weak, non-significant inverse associations

[216] O'Keefe PW, Smith RM. PCB capacitor/transformer accidents. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier, 1989.
[217] IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, Vol. 98: Painting, Firefighting, and Shiftwork. Lyon: IARC, 2010. Ruokojärvi P, Aatamila M, Ruuskanen J. Toxic chlorinated and polyaromatic hydrocarbons in simulated house fires. Chemosphere 2000; 41: 825–828.
[218] Bush B, Bennett AH, Snow JT. Polychlorobiphenyl congeners, p,p'-DDE, and sperm function in humans. Arch Environ Contam Toxicol 1986; 15: 333-341.
[219] Bonde JP, Toft G, Rylander L, Rignell-Hydbom A, Giwercman A, Spano M, Manicardi GC, Bizzaro D, Ludwicki JK, Zvyezday V, Bonefeld-Jørgensen EC, Pedersen HS, Jönsson BA, Thulstrup AM. Fertility and markers of male reproductive function in Inuit and European populations spanning large contrasts in blood levels of persistent organochlorines. Environ Health Perspect 2008; 116: 269-277.
[220] Spano M, Toft G, Hagmar L, Eleuteri P, Rescia M, Rignell-Hydbom A, Tyrkiel E, Zvyezday V, Bonde JP. Exposure to PCB and p, p'-DDE in European and Inuit populations: impact on human sperm chromatin integrity. Human Reprod 2005; 20: 3488-3499.

with testicular size and Tanner stage. DDE was highly correlated with PCB and showed slightly weaker associations with the hormone profile.[221]

Effects on female reproduction

In an Inuit population in Canada a significant association was observed between for example PCB-153 and shorter duration of pregnancy and reduced fetal growth.[222]

A study in the USA showed an association between higher PCB (especially PCB153) levels in serum in the general population and a double risk of early pregnancy loss in women undergoing *in vitro* fertilization and intracytoplasmic sperm injection.[223]In a study from Japan PCBs (sum of 10 congener groups) decreased the placental syncytiotrophoblast (ST) volume and increased Placental Growth Factor (PlGF) in the placenta of normal pregnancy. These results demonstrated that the human placenta, including ST, is a target of PCB toxicity, and it was concluded that current environmental PCB exposure levels are a risk to reproductive health.[224]

Effects on infant birth weight and development

Many studies but not all have indicated that maternal exposure to PCB may decrease the birth weight of her newborns. In a cohort of Michigan fish eaters reduced birth weights was observed only in the most exposed with ≥25 µg PCB/L serum measured with an old analytical method.[225]

In a group of 99 women trying to become pregnant the mean serum concentration of PCB (76 congeners) before pregnancy was a little higher than during pregnancy (5.6 and 4.7 ng/g serum).[226] Regarding exposure to anti-estrogenic PCBs (PCB 77/110, 105, 114, 126, 156/171 and 169) a substantial reduction (429 gram) in birth weight was seen in the most exposed mothers; an effect stronger than for cigarette smoking.

A meta-analysis within 12 European birth cohorts from 1990 through 2008 including almost 8000 women concluded that low-level PCB exposure impairs fetal growth.[227] On average the birth weight declined 150 gram per 1 µg/L increase in PCB-153 (indicator) in cord serum. The median level of PCB-153 in cord serum was 140 ng/L.

Breast-feeding has been linked to slowed postnatal growth. At 18 months Faroese children, who had exclusively been breast-fed for at least 6 months, weighed 0.59 kg less and were 1.5 cm shorter than those

[221] Grandjean P, Grønlund C, Kjær IM, Jensen TK, Sørensen N, Andersson AM, Juul A, Skakkebæk NE, Budtz-Jørgensen E, Weihe P. Reproductive hormone profile and pubertal development in 14-year-old boys prenatally exposed to polychlorinated biphenyls. Reprod Toxicol 2012; 34: 498-503.
[222] Dallaire R, Dewailly É, Ayotte P, Forget-Dubois N, Jacobson SW, Jacobson JL, Muckle G. Exposure to organochlorines and mercury through fish and marine mammal consumption: Associations with growth and duration of gestation among Inuit newborns. Environ Int 2013; 54: 85–91.
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[225] Karmaus W, Zhu X. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: a cohort study. Environmental Health2004; 3(1): 1-9.
[226] Murphy LE, Gollenberg AL, Buck Louis GM, Kostyniak PJ, Sundaram R. Maternal serum preconception polychlorinated biphenyl concentrations and infant birth weight. Environ Health Perspect 2010; 118: 297-301.
[227] Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, Chevrier C, Eggesbø M, Guxens M, Krämer U, Legler J, Martínez D, Palkovicova L, Patelarou E, Ranft U, Rautio A, Petersen MS, Slama R, Stigum H, Toft G, Trnovec T, Vandentorren S, Weihe P, Kuperus NW, Wilhelm M, Wittsiepe J, Bonde JP. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): A meta-analysis within 12 European birth cohorts. Environ Health Perspect 2012; 120: 162-170.

not breast-fed.[228] Intake of highly contaminated fish being very common on the Faroe Islands .The concentrations of mercury and PCB in the milk were supposed to be involved, and a doubled PCB concentration in the milk was 42 months associated with a decrease in weight by 0.3 kg and in height by 63 cm.

Neurophysiological effects and neurotoxicity

The developing fetus and infants are most vulnerable to exposure for PCB. There is growing evidence that PCB may affect transient neurodevelopment and neuropsychological function in children.[229]

There was evidence of deficits in attention in children exposed to PCB prenatally and non-elicited activity in postnatally exposed with the strongest association during 4th month of life.[230]

This corresponds with the findings in a Japanese study, in which prenatal exposure to the dioxin-like PCB118 seemed to influences fixation duration on biological motion at 4-months after birth.[231]

Associations have been reported between prenatal (cord blood serum) PCB and *p,p´*-DDE levels and teacher-reported behaviors related to attention deficit hyperactivity disorder (ADHD) among 8-year-old children born to mothers residing adjacent to a PCB-contaminated harbor in New Bedford, Massachusetts (USA).[232] This children cohort was later studied with standardized neurophysiological tests of attention and impulse control. The outcome supported an association between especially PCBs and neuropsychological measures of inattention in boys only.[233]

A recent study from Barcelona, Spain, increasing prenatal PCB-153 concentrations were associated with worse mental and psychomotor development.[234] The results of the study suggested that, although breastfeeding increased with children's blood levels of persistent organic pollutants (POPs) during postnatal life, the deleterious effects of PCB-153 on neuropsychological development were mainly attributable to the effect of prenatal lower level exposures on early brain development.

The prenatal exposure to PCBs (75 congeners) was measured in placental tissues, and >50 potential predictors of intelligence (IQ) at 9 years of age were measured in 156 subjects from Oswego, New York. The results indicated that prenatal PCB exposure in the Great Lakes region is associated with lower IQ in children.[235]

Thyroid dysfunction may be a mediator of organochlorine neurotoxicity in preschool children. A population-based birth cohort of 182 children from the Faroe Island was followed annually up to 5.5 years of age. The

[228] Grandjean P, Budtz-Jørgensen E, Steuerwald U, Heinzow B, Needham LL, Jørgensen PJ, Weihe P. Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. The FASEB Journal 2003; 17: 699-701.
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[231] Doi H, Nishitani S, Fujisawa TX, Nagai T, Kakeyama M, Maeda T, Shinohara K. Prenatal exposure to a polychlorinated biphenyl (PCB) congener influences fixation duration on biological motion at 4-months-old: a preliminary study. PLoS One. 2013; 8(3):e59196.
[232] Sagiv SK, Thurston SW, Bellinger DC, Tolbert PE, Altshul LM, Korrick SA. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. Am J Epidemiol 2010; 171:593-601.
[233] Sagiv SK, Thurston SW, Bellinger DC, Altshul LM, Korrick SA. Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines. Environ Health Perspect 2012; 120: 904–909.
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[235] Stewart PW, Lonky E, Reihman J, Pagano J, Gump BB, Darvill T. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. Environ Health Perspect 2008; 116: 1416-1422.

assessments included OC concentrations in maternal pregnancy serum and milk, clinical thyroid parameters in maternal and cord serum, and subsequent neuropsychological outcomes of the child, along with socio-demographic cofactors. It was observed that environmental exposures to PCBs and related substances diminished resin triiodothyronine uptake ratio in pregnant women and newborns, although it does not seem to interfere directly with the concurrent thyroxine levels. Furthermore, slight changes in tri-iodo-thyronine uptake ratio (T3UR) and some thyroid parameters are associated with child neurodevelopment during subsequent years.[236]

PCB may be a risk factor in Parkinson's disease. Animal experiments have shown that PCB mixtures can decrease the expression of dopaminergic markers. The PCB-153 concentration was elevated in post-mortem human brains from Parkinson patients,[237] and a cohort of heavily PCB-exposed female workers had increased risk for catching this disease, dementia and amyotrophic lateral sclerosis.[238] In a recent study of PCB concentrations (PCB28, PCB101, PCB118, PCB138, PCB149, PCB153, PCB170, PCB180) in post-mortem brain samples, the female Parkinson's disease group demonstrated significantly elevated concentrations of total PCBs and specifically for the most abundant congeners PCB138, PCB153, and PCB180 compared to controls. In comparison, PCB concentrations in males were not significantly different between the control group and the Parkinson's disease group.[239] The mechanism may be that NDL-PCBs inhibit the dopamine transporter.[240]

Endocrine disruption

Exposure to dioxins and PCB has been suggested to disrupt gonadal steroidogenesis and neuroendocrine pathways.[241]

The Duisburg birth cohort was initiated in 2000 with 232 participants. In subsamples of 104 mother-infant pair's dioxins, DL-PCBs and NDL-PCBs (the six DIN congeners) were measured in maternal blood during pregnancy and in maternal milk. Further, testosterone and estradiol levels were measured in maternal and cord serum. A reduction of hormone levels in serum was associated with dioxins and DL-PCBs, and testosterone reduction was more pronounced in cord serum of female and estradiol reduction in that of male newborns.[242] A later study of the Duisburg birth cohort from 2000 showed that PCDD/F and DL-PCB (expressed as dioxin-equivalents) exposure in infancy via mothers milk was associated with increased dehydroepiandrosterone sulfate (DHEA-S) serum levels in pre-pubertal children (6-8 years). Increased DHEA-S serum levels were suggestive of an acceleration of the adrenal maturation.[243] A quite recent follow-up of the Duisburg cohort prenatal exposure to dioxins and PCBs in boys was associated with more

[236] Julvez J, Debes F, Weihe P, Choi AL, Grandjean P. Thyroid dysfunction as a mediator of organochlorine neurotoxicity in preschool children. Environ Health Perspect 2011; 119:1429–1435.
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[242] Cao Y, Winneke G, Wilhelm M, Wittsiepe J, Lemm F, Fürst P, Ranft U, Imöhl M, Kraft M, Oesch-Bartlomowicz B, Krämer U. Environmental exposure to dioxins and polychlorinated biphenyls reduce levels of gonadal hormones in newborns: Results from the Duisburg cohort study. Int J Hyg Environ Health 2008; 211: 30–39.
[243] Rennert,A, Wittsiepe J, Kasper-Sonnenberg M, Binder G, Fürst P, Cramer C, Krämer U,Wilhelm M. Prenatal and early life exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls may influence dehydroepiandrosterone sulfate levels at prepubertal age: results from the Duisburg birth cohort study. J Toxicol Environ Health, Part A 2012; 75: 1232-1240.

feminine behavior, while in girls exposure was associated with less feminine behavior. It was concluded that there was sufficient evidence that dioxins and PCBs as endocrine disruptors modify behavioral sexual dimorphism in children.[244]

In a study of a birth cohort in the Faroe Islands, PCB, DDE and hormonal levels of 438 boys at age 14 were analyzed in blood serum and compared with cord blood levels.[245] Higher prenatal PCB exposure was associated with lower serum concentrations of both the luteinizing hormone (LH) and testosterone. In addition, sex hormone binding globulin (SHBG) was positively associated with both prenatal and concurrent PCB exposures. Some hydroxy-metabolites of coplanar DL-PCB have a structure resembling thyroxine (T_4) and may bind to its transport proteins and reduce thyroxine levels in the blood.[246] Such metabolites were for example determined in blood serum from pregnant Faroese women.[247]

In a study of a population in Germany around a toxic waste incinerator a significant positive association was found with the mono-ortho PCB118 and TSH as well as a negative relationship of PCBs (PCB138, 153, 180, 183 and 187) to free triiodothyronine (FT_3) - but not to free thyroxine (FT_4).[248]

Recently, Relative Effect Potency (REP) of dioxin-like activity (AhR receptor binding) for DL-PCBs in adults has been estimated based on two thyroid endpoints (thyroid gland volume and free thyroxine (FT_4) in serum).[249]

Effects on obesity

In 2002 biochemist Paula F. Baillie-Hamilton from Stirling University in Scotland was the first to explain the current global obesity epidemic with our exposure to chemicals (obesogens) in the environment and food.[250] Later an increasingly number of studies indicated that she her premise might be right, and it is now documented that background levels of PCB may affect body size of white girls at puberty.[251]

Obesity is characterized by adipocyte hypertrophy but also by the accumulation of macrophages in adipose tissue (AT) depots. Accumulation of macrophages in the visceral AT depot, but not the subcutaneous depot, is associated with liver injury. AT is classically viewed as the main reservoir of energy mobilized from the body but it is also essential for normal carbohydrate and lipid homeostasis. When stimulated by insulin, adipocytes store glucose as triglycerides in lipid droplets. Adipocytes meet the energy needs in states of metabolic stress, such as fasting, by releasing fatty acids through lipolytic processes. In addition to the energy-storing function of AT, adipocytes secrete several endocrine factors such as leptin and adiponectin,

[244] Winneke G, Ranft U, Wittsiepe J, Kasper-Sonnenberg M, Fürst P, Krämer U, Seitner G, Wilhelm M. Behavioral sexual dimorphism in school age children and early developmental exposure to dioxins and PCBs: A follow-up study of the Duisburg cohort. Environ Health Perspect, Advance Publication: 22 November 2013. Http://dx.doi.org/10.1289/ehp.1306533

[245] Grandjean P, Grønlund C, Kjær IM, Jensen TK, Sørensen N, Andersson AM, Juul A, Skakkebæk NE, Budtz-Jørgensen E, Weihe P. Reproductive hormone profile and pubertal development in 14-year-old boys prenatally exposed to polychlorinated biphenyls. Reprod Toxicol 2012; 34: 498–503.

[246] Brouwer A, Morse DC, Lans MC, Schuur AG, Murk AJ, Klasson-Wehler E, Bergman A, Visser TJ. Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. Toxicol Ind Health 1998; 14: 59-84.

[247] Fängström B, Athanasiadou M, Grandjean P, Weihe P, Bergman Å. Hydroxylated PCB metabolites and PCBs in serum from pregnant Faroese women. Environ Health Perspect 2002; 110: 895–899.

[248] Osius N, Karmaus W, Kruse H, Witten J. Exposure to Polychlorinated Biphenyls and Levels of Thyroid Hormones in Children. Environ Health Perspect 1999; 107: 843-849.

[249] Trnovec T, Jusko TA, Šovčíková E, Lancz K, Chovancová J, Patayová H, Palkovičová L, Drobná B, Langer P, Van den Berg M, Dedik L, Wimmerová S. Relative Effect Potency Estimates of Dioxin-like Activity for Dioxins, Furans, and Dioxin-like PCBs in Adults Based on Two Thyroid Outcomes. Environ Health Perspect 2013; 121: 886-892.

[250] Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. Altern Complement Med 2002; 8: 185-192.

[251] Gladen BC, Ragan NB, Rogan WJ. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. J Pediatr 2000; 136: 490–96.

which regulate appetite as well as metabolic and inflammatory functions. Adipose tissue is the main storage location for persistent and lipophilic chemicals (POPs) such as PCB and can protect other critical organs from POPs overload. Thus it plays diverse functions both as a modulator and as a target of POPs toxicity.[252]

A study from Belgium found an association between increasing concentrations of PCB (and DDE) in cord blood and in increasing Body Mass Index (BMI) of 1-3 years old children.[253]

A study of the Swedish Uppsala cohort (PIVUS) of 1016 persons aged 70 years from April 2001 to June 2004 and re-investigated at 75 years showed a positive association between PCB105 and PCB118 in blood plasma and in both the most harmful visceral adipose tissue (VAT) and in subcutaneous adipose tissue (SAT). Whereas the more highly chlorinated PCBs (PCB153, PCB156, PCB157, PCB169, PCB170, PCB180, PCB194, PCB206 and PCB209) were inversely related. PCB189, previously linked to diabetes, was related to the VAT/SAT ratio in an inverted U-shaped manner.[254] In another study of this cohort, high levels of the less-chlorinated PCBs at age 70 were associated with a pronounced estimated weight change (increase) over the previous 50 years. However, the opposite was seen for highly-chlorinated PCBs. Differences in mode of action, toxicokinetics, non-linear relationships and reverse causation might explain these discrepancies.[255]

A National Toxicology Program workshop (Raleigh, January 11-13, 2011) reporting about the role of environmental chemicals in diabetes and obesity concluded that there was support for the "developmental obesogen" hypothesis, which suggests that chemical exposures may increase the risk of obesity by altering the differentiation of adipocytes or the development of neural circuits that regulate feeding behavior. The effects may be most apparent, when the developmental exposure is combined with consumption of a high-calorie, high-carbohydrate, or high-fat diet later in life.[256]

Effects on diabetes

In the last years dozens of studies have reported an association between body concentrations of POPs, including PCBs and the metabolic syndrome, insulin sensitivity and insulin secretion.[257,258,259,260, 261]

[252] La Merrill M, Emond C, Kim MJ, Antignac JP, Le Bizec B, Clément K, Birnbaum LS, Barouki R. Toxicological function of adipose tissue: focus on persistent organic pollutants. Environ Health Perspect 2013; 121: 162-169.
[253] Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C, Schoeters G, Desager K. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ Health Perspect 2009; 117: 122-126.
[254] Roos V, Rönn M, Salihovic S, Lind L, van Bavel B, Kullberg J, Johansson L, Ahlström H, Lind PM. Circulating Levels of Persistent Organic Pollutants in Relation to Visceral and Subcutaneous Adipose Tissue by Abdominal MRI. Obesity 2013; 21: 413-418.
[255] Lind PM, Lee D-H, Jacobs DR, Salihovic S, van Bavel B, Wolff MS, Lind L. Circulating levels of persistent organic pollutants are related to retrospective assessment of life-time weight change. Chemosphere 2013; 90: 998–1004.
[256] Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. Environ Health Perspect 2012; 120: 779-789.
[257] Lee D-H, Jacobs DR, Porta M. Could low-level background exposure to persistent organic pollutants contribute to the social burden of type 2 diabetes? J Epidemiol Community Health 2006; 60:1006–1008.
[258] Ukropec J, Radikova Z, Huckova M, Koska J, Kocan A, Sebokova E, Drobna B, Trnovec T, Susienkova K, Labudova V, Gasperikova D, Langer P, Klimes I. High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. Diabetologia 2010; 53: 899‑906.
[259] Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P, Sun Q. Persistent Organic Pollutants and Type 2 Diabetes: A Prospective Analysis in the Nurses' Health Study and Meta-analysis. Environ Health Perspect 2013; 121: 153–161.
[260] Everett CJ, Frithsen I, Player M. Relationship of polychlorinated biphenyls with type 2 diabetes and Hypertension. J Environ Monit 2011; 13: 241–251.
[261] Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock EJ, Lillefosse H, Ma T, Pesenti S, Sonne SB, Marstrand TT, Malde MK, Du ZY, Chavey C, Fajas L, Lundebye AK, Brand CL, Vidal H, Kristiansen K, Frøyland L. Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome. Environ Health Perspect 2010; 118: 465–471.

This diabetic effect may occur at low doses similar to current human exposure levels, possibly through endocrine disruption, and may play a role in the current epidemic of type-2 diabetes, which mainly have been attributed to obesity.[262] On the other hand there does not seem to be any association between POP/PCB exposure and childhood type-1 diabetes.[263]

In one of the earlier cross-sectional studies a large birth cohort of 2245 pregnant women, including 44 with diabetes, was investigated. It was observed that the adjusted mean serum PCB level in the women with diabetes was 30% higher (3.77 µg/L) than in controls (2.79 µg/L).[264]

One of the highly PCB-exposed populations is from Anniston, Alabama, where Monsanto until 1971 had its PCB factory. A group of 774 volunteers randomly selected. The most PCB exposed quintile women had almost three fold higher risk for type-2 diabetes.[265] In people <55 years old the association was even greater. The mean PCB in serum was 6.3 ppb in normal people and 7.7 ppb in people with diabetes; 35 PCB congeners were measured.

In a study of Native Americans an almost 4 fold higher risk of type-2 diabetes in the most exposed people was observed.[266] The association with PCB74 was stronger than for PCB153.

A study of the Swedish Uppsala cohort (PIVUS) of 1016 persons aged 70 years from April 2001 to June 2004 and re-investigated at 75 years showed - after adjusting for known type-2 diabetes risk factors, including obesity, that environmental exposure to PCBs substantially increased risk of future type 2 diabetes in an elderly population.[267]

Polybrominated biphenyls (PBBs), the brominated analogue to PCBs, were a flame retardant mistakenly added to animal feedstuff in the state of Michigan causing a state-wide pollution incident in 1973. A cohort of exposed people has been followed since 1976 and surveyed again in 1991-1993 and in 2001. The 25-years follow-up showed no association between PBB and diabetes; however, in women higher PCB serum levels were associated with an increased incidence of diabetes.[268] In both men and women, overweight and obesity increased the diabetes incidence.

In the Faroe Islands the traditional seafood contains significant amounts of PCB (and mercury). People over 70 years old with type-2 diabetes or impaired fasting glycemia tended to have higher PCB concentrations and higher past intake of traditional foods.[269] In non-diabetics, the fasting insulin concentration decreased

[262] Lee DH, Steffes MW, Sjödin A, Jones RS, Needham LL, Jacobs DR Jr. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case–control study. Environ Health Perspect 2010; 118: 1235-1242.
[263] Rignell-Hydbom A, Elfving M, Ivarsson SA, Lindh C, Jönsson BA, Olofsson P, Rylander L. A Nested Case-Control Study of Intrauterine Exposure to Persistent Organochlorine Pollutants in Relation to Risk of Type 1 Diabetes. PLoS ONE 2010;5 (6): e11281.
[264] Longnecker MP, Klebanoff MA, Brock JW, Zhou H. Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. Diabetes Care 2001; 24: 1099-1101.
[265] Silverstone AE, Rosenbaum PF, Weinstock RS, Bartell SM, Foushee HR, Shelton C, Pavuk M. Polychlorinated Biphenyl (PCB) Exposure and Diabetes: Results from the Anniston Community Health Survey. Environ Health Perspect 2012; 120: 727-732.
[266] Codru N, Schymura MJ, Negoita S, Rej R, Carpenter DO. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans. Environ Health Perspect 2007; 115: 1442-1447.
[267] Lee D-H, Lind PM, Jacobs Jr DR, Salihovic S, van Bavel B, Lind L. Polychlorinated Biphenyls and Organochlorine Pesticides in Plasma Predict Development of Type 2 Diabetes in the Elderly. Diabetes Care 2011; 34, 1778-1784.
[268] Vasiliu O, Cameron L, Gardiner J, Deguire P, Karmaus W. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. Epidemiology 2006; 17: 352-359.
[269] Grandjean P, Henriksen JE, Choi AL, Petersen MS, Dalgard C, Nielsen F, Weihe P. Marine food pollutants as a risk factor for hypoinsulinemia and type 2 diabetes. Epidemiology 2011; 22: 410-417.

by 7% and conversely the fasting glucose concentration increased by 6% for each doubling of the PCB concentration showing an impaired insulin secretion.

In a recent study from Catalonia, Spain, of 886 participants in a health survey the highest concentrations of POPs analyzed were found in persons who had diabetes and prediabetes.[270] Both for persons with normal weight, overweight and obese people there was an association between increasing PCB (PCB118 + PCB138 + PCB153 + PCB180) in blood serum and type-2 diabetes. For obese persons with the highest PCB concentration the risk for diabetes was 9 fold higher.

There are indications that mitochondrial dysfunction plays a key role in the association of POPs and insulin resistance or type-2 diabetes.[271] The association between diabetes and POPs may be due to a change in the metabolism in diabetics.

A recent review of 72 epidemiological studies investigating associations between POPs and type-2 diabetes was taken into account in another report arisen from the NTP workshop mentioned above.[272] The overall evidence was considered sufficient for showing a positive association of some organochlorine POPs with type-2 diabetes. The strongest positive correlation between diabetes and POPs was found for organochlorine compounds, such as *trans*-nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), and dioxins and dioxin-like chemicals. However, collectively, these data were not sufficient to establish causality.

Effects on the immune system

Increasing evidence suggests that PCBs can cause dysregulation of the immune system through immunosuppression and immune stimulation/inflammation. Epidemiological studies show that PCBs are associated with modification of both innate and adaptive immunity, including having effects on immune cells and signaling molecules, with implications for both immune response and initiation. Such effects are manifested as an increased incidence of infections; insufficient antibody response to vaccination; and changes in immune organs, lymphocyte subsets, and lymphocyte function. Immune system dysregulation has been considered an important and well-established risk factor for Non-Hodgkin Lymphoma (NHL). There are several case-control studies showing an association with PCB exposure, especially measured as PCB118, PCB138, PCB153 and PCB180.[273]

PCB exposure, as estimated by various measures including PCB levels in cord blood, maternal sera, and breast milk, has been associated with an increased incidence of respiratory infections, ear infections, influenza, and chicken pox in healthy Dutch and Inuit preschoolers;[274,275] children of capacitor

[270] Gasull M, Pumarega J, Téllez-Plaza M, Castell C, Tresserras R, Lee DH, Porta M. Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia. Environ Sci Technol 2012; 46: 7799-7810.
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[272] Taylor KW, Novak RF, Anderson HA, Birnbaum LS, Blystone C, Devito M, Jacobs D, Köhrle J, Lee DH, Rylander L, Rignell-Hydbom A, Tornero-Velez R, Turyk ME, Boyles AL, Thayer KA, Lind L. Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: A National Toxicology Program Workshop Review. Environ Health Perspect 2013; 121: 774–783.
[273] Kramer S, Hikel SM, Adams K, Hinds D, Moon K. Current Status of the Epidemiologic Evidence Linking Polychlorinated Biphenyls and Non-Hodgkin Lymphoma, and the Role of Immune Dysregulation. Environ Health Perspect 2012; 120: 1067–1075.
[274] Weisglas-Kuperus N, Vreugdenhil HJI, Mulder PGH. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. Toxicol Lett 2004; 149:281–285.
[275] Dallaire F, Dewailly É, Vézina C, Muckle G, Weber J-P, Bruneau S, Ayotte P. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. Environ Health Perspect 2006; 114: 1301–1305.

manufacturing workers, particularly those breast-fed for lengthy periods;[276] and children prenatally exposed to PCB- and PCDF-contaminated rice oil during the Yu-Cheng poisoning incident.[277]

PCB exposure has also been associated with insufficient vaccination response in two birth cohorts from the Faroe Islands with pre- and postnatal PCB exposure from dietary consumption of whale blubber. Insufficient antibody response to diphtheria and tetanus toxoid was associated with PCB exposure with each doubling of cumulative PCB exposure associated with a 24% reduction in diphtheria antibody response at 18 months of age and each doubling of prenatal PCB exposure associated with a 16% reduction in tetanus toxoid response at 7 years of age. By 5 years of age, a doubling of PCB exposure was associated with a 30% increased odds of anti-diphtheria antibody concentrations below the limits for long-term protection.[278]

In Slovakia, a country with high background exposure for PCB, because of previous production and heavy use, it was observed in a group of 1134 mother-child pairs that high maternal PCB (15 congeners) blood concentration was associated with reduced thymus volume at birth.[279] The mean maternal PCB serum concentrations were 6 ng/mL fresh weights and 591 ng/g on lipid basis.

Asthma

There are a number of studies suggesting probable association between the incidence of asthma and the levels of PCB residues in human tissues. A study of the Faroe Islands birth cohort showed that the total IgE concentration in serum at 7 years of age was positively associated both with the concomitant serum PCB concentration and with the duration of breast-feeding suggest that developmental exposure to PCB may increase the risk of allergic disease.[280] In a newer study serum concentrations of PCB163/164, PCB170, PCB177, PCB178 and PCB180/193 correlated significantly with the marker for childhood asthma interleukin (IL-8 mRNA) expressions among 2 years old asthmatic children in Japan.[281]

Effects on cardiac system

An early study showed a positive association between PCB in blood serum and elevated blood pressure, serum cholesterol and γ-glutamyl transpeptidase level.[282]

In a study of blood serum samples from more than 3000 participants in the National Health and Nutrition Examination Survey (NHANES) 1999-2004 a significant association was observed between elevated blood pressure and serum levels of dioxin-like PCB74, PCB118 and PCB126.[283]

The residents of Anniston, Alabama, USA, have been and are still heavily PCB exposed to PCB due to historical pollution from an earlier PCB factory located there. In a recent study of 394 residents total serum

[276] Hara I. Health status and PCBs in blood of workers exposed to PCBs and of their children. Environ Health Perspect 1985; 59: 85–90
[277] Yu M-L, Hsin J-W, Hsu C-C, Chan W-C, Guo YL. The immunologic evaluation of the Yucheng children. Chemosphere 1998; 37:1855–1865
[278] Heilmann C, Budtz-Jørgensen E, Nielsen F, Heinzow B, Weihe P, Grandjean P. Serum concentration of antibodies against vaccine toxoids in children exposed perinatally to immunotoxicants. Environ Health Perspect 2010; 118: 1434–1438.
[279] Jusko TA, Sonneborn D, Palkovicova L, Kocan A, Drobna B, Trnovec T, Hertz-Picciotto I. Pre- and postnatal polychlorinated biphenyl concentrations and longitudinal measures of thymus volume in infants. Environ Health Perspect 2012; 120: 595-600.
[280] Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants. Environ. Health Perspect 2010; 118: 1429–1433.
[281] Tsuji M , Vogel CF, Koriyama C, Akiba S, Katoh T, Kawamoto T, Matsumura F. Association of serum levels of polychlorinated biphenyls with IL-8 mRNA expression in blood samples from asthmatic and non-asthmatic Japanese children. Chemosphere 2012; 87: 1228–1234.
[282] Kreiss K, Zack MM, Kimbrough RD, Needham LL, Smrek AL, Jones BT. Association of blood pressure and polychlorinated biphenyl levels. JAMA 1981; 245: 2505-2509.
[283]Everett CJ, Mainous AG, Frithsen IL, Player MS, Matheson EM. Commentary on the association of polychlorinated biphenyls with hypertension, Environ Res 2008; 108: 428–429.

PCB concentration was the strongest determinant of blood pressure of the covariates studied other than age.[284] The strongest associations were found for those PCB congeners that had multiple *ortho*-chlorines (NDL- PCBs). The associations were found over the full range of blood pressure as well as in those subjects whose blood pressure was in the normal range.

Among the heavily exposed Inuit's from Canada total PCB as well as DL-PCBs was associated with hypertension.[285]

The possible association between organic pollutants and cardiovascular disease has recently been reviewed.[286] In a study of the NHANES 1999-2002 cohort 889 participants (≥ 40 years old) were investigated regards cardiovascular diseases (CVD). PCB congeners 156 (dioxin like), 138, 153, and 170 were associated with self-reported CVD among females but not males.[287]

Increased circulating levels of persistent organic pollutants, including PCB, have been associated with myocardial infarction, an atherosclerotic disease. A Swedish cohort (PIVUS) of 1016 people from Uppsala became 70 years old in the period from April 2001 to June 2004. From March 2006 to September 2009, when the subjects became 75, a reinvestigation of the cohort was performed with a follow-up rate of 81.4%. It was shown that circulating levels of PCB congeners PCB153, PCB156, PCB157, PCB170, PCB180, PCB206, and PCB209 were associated with increased atherosclerotic plaques formation determined with ultra sound.[288] Higher chlorinated PCBs were also associated with a marker for lipid infiltration in the vascular wall, an early sign of atherosclerosis development measurable in people without plaques. Details about the PCB levels are published.[289] Circulating levels of PCB99, PCB118, PCB105, PCB138, PCB153, PCB180 and octachlorodibenzo-*p*-dioxin (OCDD) were related to impairments in both left ventricular systolic and diastolic function independently of major congestive heart failure risk factors, suggesting a possible role of POPs in heart failure.[290]

Another study of the same cohort demonstrated that plasma concentrations of POPs were strongly associated with an increased risk of developing or progression of stroke in this elderly population.[291] After adjusting for known stroke risk factors, most PCBs with 4, 5, or 6 chlorine atoms significantly predicted the risk of stroke. Across quartiles of summary measures of PCBs, the adjusted ORs were 1.0, 0.8 (95% confidence interval: 0.2–2.5), 1.2 (0.4–3.4), and 2.1 (0.7–6.2) for PCBs. The adjusted ORs among participants ≥90th percentile of the summary measures were 5.5 (1.7–18.1) for PCBs. Taken together with previous experimental and epidemiological studies, POPs may play a fundamental role in the development of stroke.

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[284] Goncharov A, Pavuk M, Foushee HR, Carpenter DO. Blood pressure in relation to concentrations of PCB congeners and chlorinated pesticides. Environ Health Perspect 2011; 119:319–325.
[285] Valera B, Ayotte P, Poirier P, Dewailly E. Associations between plasma persistent organic pollutant levels and blood pressure in Inuit adults from Nunavik. Environ Int 2013; 59: 282-289.
[286] Lind L, Lind PM. Can persistent organic pollutants and plastic-associated chemicals cause cardiovascular disease? J Intern Med 2012; 271:537-53.
[287] Ha M-H, Lee D-H, Jacobs DR Jr. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey 1999–2002. Environ Health Perspect 2007; 115: 1204–1209.
[288] Lind PM, van Bavel B, Salihovic S, Lind L. Circulating Levels of Persistent Organic Pollutants (POPs) and Carotid Atherosclerosis in the Elderly. Environ Health Perspect 2012; 120: 38-43.
[289] Salihovic S, Lampa E, Lindström G, Lind L, Lind PM, van Bavel B. Environ Int 2012; 44: 59-67.
[290] Lind YS, Lind PM, Salihovic S, van Bavel B, Lind L. Circulating levels of persistent organic pollutants (POPs) are associated with left ventricular systolic and diastolic dysfunction in the elderly. Environmental Research 2013; 123: 39–45.
[291] Lee D-H, Lind PM, Jacobs DR Jr, Salihovic S, van Bavel B, Lind L. Background exposure to persistent organic pollutants predicts stroke in the elderly. Environ Int 2012; 47: 115-120.

Liver effects

The NHANES 2003-2004 survey materials have been used to evaluate the relationship between alanine aminotransferase (ALT), which is a marker for liver effects, and 37 environmental contaminants. Concentrations of DL-PCBs, NDL-PCBs were significantly associated with elevated ALT, especially PCB180.[292]

Cancer

As mentioned elsewhere carcinogenicity is indicated in experimental animals and an occupational cancer risk of some PCB mixtures and congeners. During the years many general population studies has looked at a possible association between PCB levels in human tissues and cancer incidence/mortality.

Exposure to PCBs may be an etiologic factor for breast cancer. The cytochrome P_{450} 1B1 (CYP1B1) and catechol-*O*-methyl transferase (COMT) enzymes are involved in estrogen metabolism and PCB metabolism, both of which may relate to breast cancer susceptibility. Polymorphisms in genes regulating these enzymes control efficiency. In a Danish study of the breast cancer risk in menopausal women neither CYP1B1 Leu432Val polymorphisms nor adipose tissue PCBs were independently associated with breast cancer risk.[293]

A recent case-control study (92 cases and 92 controls) from China and published in Chinese language concluded that serum *β*-HCH, *pp'*-DDE and PCB52 levels were positively associated to the risk of breast cancer.[294]

A review of more than hundred studies of environmental chemicals and breast cancer published during 2006-2013 was presented at a recent American Public Health Association meeting. Since a previous similar study covering the years 2000-2006 the strength of evidence of polychlorinated biphenyls (PCBs) and breast cancer risk had grown, specifically showing that postpartum levels increase risk of breast cancer in younger women.[295]

IARC assessment

The International Agency for Research on Cancer (IARC) has evaluated the carcinogenic hazard of PCBs in multiple instances. In 1978, although there was no formal evaluation at the time, it was concluded that PCBs "should be considered, as if they were carcinogenic to humans".[296]

The first IARC evaluations were made in 1979 in Supplement 1, and PCBs were classified as probably carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals, and with possible target organs in humans identified as "all sites".[297]

In IARC Monographs, Supplement 7, from 1987 the evidence for carcinogenicity to humans was considered limited but there was sufficient evidence for carcinogenicity to animals, and the overall evaluation was

[292] Yorita Christensen KL, Carrico CK, Sanyal AJ, Gennings C. Multiple classes of environmental chemicals are associated with liver disease: NHANES 2003-2004. Int J Hyg Environ Health 2013; 216: 703-709.
[293] Brauner EV, Loft S, Wellejus A, Autrup H, Tjønneland A, Raaschou-Nielsen O. Adipose tissue PCB levels and CYP1B1 and COMT genotypes in relation to breast cancer risk in postmenopausal Danish women. Int J Environ Health Res 2013 Jul 22. [Epub ahead of print].
[294] Zhang H, Liu L, Zhang P, Zhao Y, Wu X, Ni W. [A case-control study on the relationship between organochlorine and female breast cancer]. Wei Sheng Yan Jiu 2013; 42: 44-48.
[295] Rodgers K, Brody JG. Environmental chemicals and cancer: A review of epidemiologic studies from 2006-2013. 141st APHA Annual Meeting and Expo. Boston, MA, November 2-6, 2013.
[296] IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 18: Polychlorinated biphenyls and polybrominated biphenyls. IARC: Lyon, 1978.
[297] IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemical and industrial processes associated with cancer in humans (IARC Monographs Volumes 1 to 20). Supplement 1. IARC: Lyon, 1979.

"probably carcinogenic to humans (2A)".[298] Data from additional animal experiments had strengthened the evidence of highly-chlorinated PCB mixtures' ability for induction of liver tumors in rodents. In addition, it had been shown that PCB may enhance/promote the incidence of tumors induced by well-known carcinogens, such as nitrosamines.[299]

More recently, in 2012, in the frame of the reevaluation of 2,3,7,8-tetrachlorodibenzodioxin (TCDD), the congener PCB126 (3,3',4,4',5-pentachlorobiphenyl) was classified as carcinogenic to humans (Group 1) on the basis of a strong similarity with TCDD in the mechanism of carcinogenesis.[300]

At the most recent evaluation, 12-19 February 2013, the Working Group concluded that there was sufficient evidence of carcinogenicity in humans, and PCBs were classified as carcinogenic to humans (Group 1). In addition, dioxin-like PCBs were also classified in Group 1 based on strong evidence for multiple mechanisms of carcinogenesis. This re-evaluation is supposed to be published in IARC Monographs vol. 107 but a summary of the evaluation has been published.[301]

The re-evaluation of PCBs considered the mixture of congeners, since the carcinogenicity is not known to be limited to a small number of congeners, and because human exposures to PCBs, whether from indoor air or from other sources, always involve mixtures of many congeners. Thus, although IARC does not consider source attribution in their evaluations, the current classification of PCBs also applies to exposures from construction materials, which may be one of the important sources of exposure.

In their assessment the Working Group considered more than 70 independent epidemiological studies with informative data for carcinogenicity of PCBs in human beings. Excess risks for melanoma were reported consistently in several studies, mainly cohort studies of workers in the manufacture of capacitors and transformers, and in electric power and equipment maintenance. A significant linear exposure–response relationship was noted in the largest study.[302] In a population-based case-control study that assessed exposure with PCB serum levels, the association persisted after control for sun sensitivity and exposure.[303]

The carcinogenicity of PCBs in animals was assessed for individual congeners; binary mixtures of congeners; technical mixtures containing various congeners; and simulated environmental mixtures, with 2 year bioassays; studies with perinatal and postnatal exposure; and studies that examined the initiating and promoting activities of PCBs. Individual congeners (PCB118, PCB126) and several commercial products with a high chlorine content (Aroclor 1254, Aroclor 1260, Kanechlor 500) induced benign and malignant tumors of the liver, lung, and oral mucosa in rats; these studies provided sufficient evidence of carcinogenicity in experimental animals.

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[298] IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Overall evaluations of carcinogenicity: An updating of IARC Monographs Volumes 1 to 42: Supplement 7. IARC: Lyon, 1987.
[299] Hemming H, Bager Y, Flodstrom S, Nordgren I, Kronevi T, Ahlborg UG, Wärngård L. Liver tumour promoting activity of 3,4,5,3',4'-pentachlorobiphenyl and its interaction with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Eur J Pharmacol 1995; 292: 241.249.
[300] IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume100F. A review of human carcinogens: Chemical agents and related occupations. Lyon: IARC, 2012. http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php
[301] Lauby-Secretan B, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. Lancet Oncology 2013; 14:287-288.
[302] Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Environ Med 1997; 54: 720–728.
[303] Gallagher RP, Macarthur AC, Lee TK, Weber JP, Leblanc A, Mark Elwood J, Borugian M, Abanto Z, Spinelli JJ. Plasma levels of polychlorinated biphenyls and risk of cutaneous malignant melanoma: a preliminary study. Int J Cancer 2011; 128**:** 1872–1880.

7. Risk assessment and management

Humans are exposed to PCB from many sources and through many activities. For the general population 80-90 % of the total intake will be from food intake but in some instances other oral intakes of dusts or through inhalation of air and skin contact may increase in relative importance. That is especially the case with exposure to indoor PCB pollution or in the work environment.

Concerning PCB in the indoor environment it can be assessed and managed in different ways. Sweden, one of the pioneers, chose to base their actions on the levels of PCB in the sealing in the buildings and decided an action limit of 500 ppm in the materials for renovation. This method is very simple in regards to sampling, relative inexpensive to analyze because of high PCB levels, and the control is relative easy. Sweden should have finished its PCB building renovation program in 2013 but the last deadline has been extended to June 30, 2016.[304]

In Germany (and Denmark) another approach was selected with establishment of action limits for PCB in indoor air to take into account the present exposure of people using the buildings. However, indoor air measurements of low PCB concentrations are relatively complex, time-consuming and expensive. Further, temperature and ventilation variations may make results difficult to interpret.

In addition to the action limits for indoor air Germany has also introduced human biomonitoring of PCB in blood and breast milk to value and control the indoor PCB exposure. Many of the studies of PCB in blood and breast milk have been discussed above.

The Commission Human-Biomonitoring in the German EPA has established science-based limit values for PCB in blood serum, and if these values are not exceeded, no health risk was considered to appear.[305] The sum of PCB138 + PCB1153 + PCB180 multiplied with a factor 2 to get total PCB was recommended to make these assessments. In regards to the risk group of babies, infants, and females in the reproductive age the HBM-I value was set to 3.5 µg PCB_{total}/ L serum, and the HBM-II-Wert for other groups was 7 µg PCB_{total}/ L serum. Since the lower chlorinated PCBs are most abundant in indoor air and not included in the total PCB, these limit values is based on food intake and may not be relevant for assessment of PCB exposure indoors.

EFSA has recently concluded that a health based guidance value for humans cannot be established for NDL-PCB because simultaneous exposure to NDL-PCB and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on effects of individual NDL-PCB congeners is rather limited. However, there are indications that subtle developmental effects, being caused by NDL-PCB, DL-PCB, or polychlorinated dibenzo-*p*-dioxins polychlorinated dibenzofurans alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals and some European (sub)-populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCB in food is warranted.[306]

[304] http://www.naturvardsverket.se/Stod-i-miljoarbetet/Vagledning-amnesvis/PCB/PCB-sanera-byggnader/

[305] Bekanntmachung des Umweltbundesamtes. Human-Biomonitoring- (HBM)- Werte für Polychlorierte Biphenyle (PCB) im blut. Stellungnahme der Kommission Human-Biomonitoring des Umweltbundesamtes. Bundesgesundheitsbl 2012; 55:1069–1070..

[306] Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to the presence of non dioxin-like polychlorinated biphenyls (PCB) in feed and food. The EFSA Journal 2005; 284: 1 – 137.

7.1 Comparison of total PCB intakes with or without indoor exposures

In the ATSDR monograph the average intake of PCB with indoor air and dust have been calculated, and the health risk has been estimated.[307] If a person with a body mass of 60 kg daily inhales 15 m^3 air per day of air with a PCB concentration of 1 µg/m^3. Thus, the resulting exposure is 15 µg PCB/person or 250 ng/kg body weight/day. This is approximately 100 fold below the no-observed-adverse-effect-level (NOAEL) of 30 000-40 000 ng PCB/kg body weight/day for effects on the liver and the thyroid gland observed in 90-days oral toxicity studies with rats for three non-dioxin-like PCB.

In regards to intake of PCB in indoor dust, a daily intake of 50 mg dust and a PCB concentration of 2 µg PCB/g dust were assumed. The resulting exposure is then 0.1 µg/person or 2 ng/kg body weight/day. The detailed analysis showed congener composition in the dusts like the original commercial mixtures. For these mixtures animal tests have showed a lowest-observed-adverse-effect (LOAEL) level of 5 µg/kg body weight/day. This LOAEL is more than 3500 fold higher than the estimated highest daily intake of indoor dust.

A publication from Great Britain found a daily average total PCB intake of 0.49 µg/person/day for adults of which 30.6% (4.2 - 63%) was derived from inhalation exposure. The average intake of toddlers was 0.22 µg PCB/toddler/day, with ~12.6% from inhalation.[308] It was considered very well possible that under certain circumstances the intake from inhalation exposure may currently be the major source of PCB intake for humans.

A German study reported air levels of up to 23 000 ng PCB/m^3 in telephone centrals and 3300 ng/m^3 in a house with PCB containing sealants.[309] At exposure to air levels up to 100 ng PCB/m^3 food was considered the major exposure but since the food PCB levels nowadays are decreasing, the indoor exposure will be relatively more important. The authors criticized the present German action limits for not taking enough account for PCB's carcinogenic effect and the dioxin-like PCBs and suggested 10 fold lower values.

The PCB average intake via food in Denmark has recently been estimated to 9 ng PCB/kg bw/day or 630 ng PCB/ day for an adult person weighing 70 kg. In case of exposure to indoor air concentrations of 300-3 000 ng PCB/m^3, and if a person inhales 20 m^3 air daily during presence in the room, then the intake with indoor air will be 6 000-60 000 ng PCB_6 or 10-100 fold the food intake. In praxis most people will stay indoors in the building shorter time.

However, intake from food and indoor air cannot directly be compared because of the different congeners present and the indoor exposure is extra. WHO has recommended a tolerable daily intake (TDI) of 20 ng PCB/kg b. w., which was derived from a LOAEL of 5 µg/kg bw in monkeys exposed to a commercial mixture of PCBs (Aroclor 1254), and EU has established a tolerable weekly intake (TWI) of 14 pg TEQ/kg bw for dioxin-like-PCBs. Dietary exposure in Denmark to dioxins and DL-PCB as well as to NDL-PCB exceeds the TDI/TWIs for a small fraction of the population, and mainly for children.

[307] Toxicological Profile for Polychlorinated Biphenyls. Atlanta: ATSDR, November 2000.
[308] Harrad S, Hazrati S, Ibarra C. Concentrations of polychlorinated biphenyls in indoor air and polybrominated diphenyl ethers in indoor air and dust in Birmingham, United Kingdom: implications for human exposure. Environ Sci Technol 2006; 40: 4633–8.
[309] Ludewig S, Kruse H, Wassermann O. Zur Toxizität polychorierter Biphenyle (PCB) – Innenraumbelastung durch PCB-haltige dauerelastische Dichtungsmassen. Gesundh-Wes 1993; 55: 431-439.

7.2 Indoor actions values for PCB

In 1996 action values for 24 hours indoor exposure to PCB was established in Germany. Annual mean action value was 300 ng/m^3, and intervention value was 3000 ng/m^3 (3 µg/m^3). The PCB concentration was calculated as PCB_6 multiplied with a corrections factor of 5.[310]

The health authority in Schleswig-Holstein has developed more detailed recommendations as a supplement to the action values (see Table 7.1).[311]

Table 7.1: Recommended PCB sanitation activities by the health authority in Schleswig-Holstein.

Measured indoor air PCB concentration, ng/m^3	**Recommended sanitation activities**
<100	Regularly airing or ventilation
100-300	Extensive dust cleaning and careful room cleaning and washing of all surfaces, repeated every 6 to 12 months.
300-1000	Short-term: special cleaning by professionals before 6 months. Control measurement 3 days after cleaning to ensure PCB levels below 300 ng/m^3. Long-term: If the cleaning is not sufficient, then PCB renovation should be undertaken within 3 years to reach PCB levels below 300 ng/m^3.
1000-3000	Short-term: special cleaning as above but it will probably not solve the problem. Middle-term: Building renovation with removal of primary PCB sources and treatment of secondary sources within a year with the goal of PCB levels below 300 ng/m^3.
>3000	Immediate special cleaning and development of a renovation plan to reach PCB levels below 300 ng/m^3.

The toxicological basis was an older TDI for technical PCB mixture of 1-3 µg PCB/kg bw/day derived from rat experiments. Air concentrations were calculated based on 60 kg bw and an inhalation rate of 20 m^3/24 hours.

Later studies have shown that PCB has adverse effects in rats exposed to 900 ng PCB/m^3, and adverse effects in monkeys having a daily intake of 5 µg PCB/kg/day. Referring to those studies and applying a safety factor a tolerable resorbed dose (TRD) of 15 ng PCB/kg/day was developed as limit value for soil contamination in Germany.

In Switzerland a maximal tolerable annual mean value for indoor home exposure to PCB was set at2 µg/m^3 and at 6 µg/m^3 for exposures in schools and other institutions, respectively.[312] The same analytical method used as in Germany.

[310] Richtlinie für Bewertung und Sanierung PCB-belasteter Baustoffe und Bauteile in Gebäuden (PCB-Richtlinie). Mitteilungen Deutsche Institut für Bautechnik 1995; 26: 50-60. http://www.dibt.de/

[311] Landesamt für Gesundheit und Arbeitssicherheit des Landes Schleswig-Holstein. PCB in öffentlichen Gebäuden. http://www.schleswig-holstein.de/LASD/DE/Gesundheitsschutz/MSGFGesundheitsschutz/Schadstoffbelastung/oeffentlGebaeudePCB__blob=publicationFile.pdf

[312] http://www.bag.admin.ch/themen/chemikalien/00228/00512/index.html?lang=de

After a comprehensive health assessment of PCB in indoor air, Halberlah and coworkers (2002) proposed a toxicological based limit value for indoor air of between 10 and 200 ng/m^3, depending duration of stay in the room.[313]

Birger Heinzow and coworkers have shown that at a concentration of 1000 ng PCB_{total} /m^3, there will also be a concentration of dioxin-like PCBs ranging 0.3-0.6 pg TEQ_{WHO}/m^3. The authors proposed that the German action limit for PCB_6 in indoor air was supplemented with an action value for dioxin-like PCBs of 0.4 pg TEQ/m^3 and an intervention value of 4 pg TEQ/m^3.[314]

In 2009 the Danish National Board of Health (now called the Danish Health and Medicines Authority) introduced two recommended action levels for PCB in indoor air.

1. Levels >3000 ng/m^3 caused immediate need for action, and
2. Exposure to levels between 300 and 3000 ng/m^3 were considered to be a possible health risk and an action plan would be needed to bring levels down.

It was later specified that levels between 2000 and 3000 ng/m^3 required action before a year and lower levels within two years.[315]

USEPA has established a site-specific action level of 50 ng PCB/m^3, which requires further investigations, and an acceptable long-term average exposure concentration of 300 ng/m^3.[316]

Regards schools EPA recommends that the concentrations of PCBs in indoor air be kept as low as is reasonably achievable and that total PCB exposure be kept below the reference dose level (RfD) of 20 ng PCB/kg bw/day. The following Public Health Levels of PCBs in Schools which take into account the exposure time should manage that (see Table 7.2).[317]

Table 7.2: Public Health Levels of PCBs in school indoor air (ng/m^3)

Age 1-<2 yr	Age 2-<3 yr	Age 3-<6 yr	Age 6-<12 yr Elementary School	Age 12-<15 yr Middle School	Age 15-<19 yr High School	Age 19+ yr Adult
70	70	100	300	450	600	450

[313] Kalberlah F, Schulze J, Hassauer M, Oltmanns J. Toxikologische Bewertung polychlorierter Biphenyle (PCB) bei inhalativer Aufnahme. Materialien 62. Landesumweltamt NRW, Essen, 2002. http://www.landesumweltamt.nrw.de/veroeffentlichungen/materialien/mat62/mat62.pdf
[314] Heinzow B, Mohr S, Ostendorp G, Kerst M, Körner W. PCB and dioxin-like PCB in indoor air of public buildings contaminated with different PCB source-deriving toxicity equivalent concentrations from standard PCB congeners. Chemosphere 2007; 67: 1746-1753.
[315] http://www.sst.dk/~/media/Sundhed%20og%20forebyggelse/Indeklima%20og%20skimmelsvamp/bilag-risiko-endelig1.ashx
[316] Sullivan DM, Hunt GT, Alfonse S. Polychlorinated biphenyls (PCBs) and indoor air: source investigation and remedial approach for a public school building in New Bedford, Massachusetts, USA. Organohalogen Compounds 2008; 70: 850-854.
[317] http://www.epa.gov/wastes/hazard/tsd/pcbs/pubs/caulk/health_levl.htm

8. Conclusions

Introduction

Polychlorinated biphenyls (PCB) is a family of 209 single chlorinated substances (congeners = isomers + homologues) with different physical-chemical properties depending on chlorine content and molecular structure. The structure of PCB consists of two connected benzene rings (biphenyl), in which one or more of the 10 hydrogen atoms are substituted by chlorine.

All the 209 PCB congeners do have a specific IUPAC number starting with PCB1 for 2-chlorobiphenyl, increases with degree of chlorination. This IUPAC number is often used as quick identification instead of the longer full systematic names, which may be difficult to remember, for instance PCB153 is used instead of 2,2',4,4',5,5'-hexachlorobiphenyl.

The accumulated World production of commercial PCB mixtures has been estimated to be over 1 million tons. These products were complex mixtures of more than 100 PCB congeners in different concentrations. All these commercial PCB mixtures were very stable oils, insoluble in water, inflammable and electrically insulating and good conductors of heat. These properties were the reason for the previous main use of PCB as insulation oils in "closed" electrical equipment, such as electrical transformers and capacitors of various sizes.

PCB is a persistent organic pollutant and banned in the Stockholm convention, because it is hazardous and has become wide-spread in the global environment (air, water and soil) and accumulates in wildlife, food chains and in human tissues. Measurements of PCB in environmental samples include often 6 or 7 of the most abundant PCB congeners as an indicator of PCB. The six indicator congeners (short expression: PCB_6) are PCB28, PCB52, PCB101, PCB138, PCB153 and PCB180. The seventh congener, sometimes included, is PCB118. Total-PCB concentration in a sample can afterwards be estimated by multiplication of PCB_6 or PCB_7 with a factor of five.

The most toxic PCB congeners have a co-planar conformation similar to that of dioxin and are called dioxin-like PCBs (DL-PCBs). They bind to the same Aryl Hydrocarbon Receptor (AhR) as dioxins and have similar toxicological mechanism, and their concentration is often expressed as dioxin-toxicity-equivalents (TEQs) as with dioxin. The most potent dioxin-like PCBs are PCB77, PCB81, PCB126 and PCB169. Some mono-*ortho*-substituted congeners do also have a weak dioxin-like effect, for example PCB118. The six indicator congeners and most others are non-dioxin-like (NDL-PCBs).

PCB in buildings and indoor air

Previously, PCB mixtures were often used as stabilizer or fire retardant in hydraulic- and heat-transfer liquids and until the mid-1970s also in various open-ended systems, such as paint, lacquers and putty, elastic sealing and caulking materials in buildings. The total PCB use in Denmark in the period 1950-1983 has been estimated to 1100-2000 tons.

Today high levels of PCB are still found in caulking/sealing materials from more than 10% of the Danish buildings constructed in the period from the 1950s to about 1975. The PCB content in the materials, which are considered primary indoor pollution sources, can be up to 70% but is more often around 10%. In

Sweden, caulking joints in buildings with rented apartments shall be removed, if it contains more than 0.5% (500 ppm) PCB, and afterwards substituted by non-PCB caulking.

PCB congeners do have relatively low volatility which decreases with increasing chlorine content. In rural areas the background PCB concentration in air is very low and between 0.1 -0.2 ng PCB/m^3. In urban areas concentrations are often 10 fold higher than in rural areas, and PCB levels indoors are in general again about 30 fold higher than outdoors. PCB in indoor air of non-contaminated flats is typically much less than 30 ng PCB/m^3 measured as PCB_6 or PCB_7, and the air concentration in non-renovated contaminated flats are in general 50-100 folds higher, and higher than the Danish EPA limit value of 100 ng PCB/m^3 for industrial air emissions.

The PCB concentration in ambient air may be 50 fold greater on a hot summer day than in a cold winter day. Also PCB concentrations in indoor air depend on the temperature and are higher in the summertime.

The PCB congeners reported most often in outdoor and indoor air are PCB52 and PCB28, the two most volatile congeners among the 6 or 7 indicator PCBs but these are not alone. There are many other volatile PCB congeners in indoor air, which are not generally measured. The low-volatile congeners will dominate in indoor air polluted by elastic sealants but when the source is building materials fire-retarded with highly chlorinated PCB mixtures the less volatile indicator PCBs such as PCB138, PCB153 and PCB180 will dominate.

Reduction of indoor PCB

PCB can migrate from the sealing 30 mm into adjacent materials, such as plaster, concrete and bricks and to a less extent into wood. These contaminated materials are secondary PCB indoor pollution sources. Some Danish case studies have shown that frequent vacuuming, dusting off and washing the floor, furniture, walls and ceilings temporarily can reduce high indoor air concentrations of PCB 2-3 fold. Ventilation will also decrease air PCB levels temporarily by diluting polluted indoor air with less polluted ambient air but when ventilation ceases the PCB levels will slowly increase again by evaporation from primary, secondary and tertiary sources.

Cleaning combined with ventilation is not reported to be sufficient to bring indoor PCB concentrations below 300 ng/m^3 in settings, where the initial levels are high. In order to decrease the indoor PCB concentration further, primary, secondary and tertiary sources have to be removed and enclose eventual residues for instance with foils or active carbon impregnated wallpaper. With such combined mitigation methods it has been possible to reduce indoor air PCB concentration to < 100 ng/m^3.

Human exposures to PCB

Everybody is exposed daily to low levels of PCB in the food from the natural food chain accumulation in fatty tissues of fish and domestic animals, and for the general population the food intake is considered to contribute to 80-90% of the total intake of PCB. In 2012 EU has established Action and maximum levels of dioxins, dioxins + DL-PCBs and for NDL-PCBs in most foodstuffs.

The average daily food intake of PCB in the EU has been estimated to be between 10 and 45 ng/kg b. w. corresponding to 0.6-2.7 µg/day for a person weighing 60 kg. The most recent Danish intake estimate is a mean daily exposure to PCB of 9 ng/kg b. w. and a maximum of 82 ng/kg b. w.

In addition to the food intake of PCB, some people will be exposed heavily to indoor PCB sources in homes, offices and institutions (schools, child care homes). However, it has to be underlined that the PCB congener pattern in food is much different from the pattern in air. In food the most abundant congeners are the most persistent and bioaccumulative ones, and that are the higher chlorinated not so volatile congeners, such as PCB138, PCB153 and PCB180.

Human body burden of PCB

PCB congeners are lipophilic (attracted to fats), and after absorption PCB will circulate in the blood associated with lipoproteins. From the blood serum PCB is distributed further to fat-rich body compartments in which PCB accumulate associated with lipids, and the highest PCB concentrations are normally found in adipose tissues, which typically can have lipid contents of around 80%. In adipose tissues PCB is stored away from more critical targets such as the liver and brain. More than 60% of the background concentration of PCB in human tissues consists of the seven PCB congeners: PCB28, PCB74, PCB118, PCB138, PCB153, PCB170 and PCB180. Most abundant is PCB-153 with 10-30% of the total content. If additional exposure e.g. from indoor air is present the congener profile may change.

PCB in blood from indoor exposure

In one of the first studies from Sweden concluded that persons living in PCB contaminated apartments had about twice so much PCB in the blood as persons living in uncontaminated apartments, and specifically PCB28 in blood was 30 fold higher. In a German study of a PCB contaminated school PCB_6 was analyzes but only PCB28, PCB52 and PCB101 were detected in the air. The same congeners were also detectable in most blood samples from pupils from the contaminated schools but only in a few of the samples from non-contaminated schools. The blood levels of PCB52, PCB101 and PCB28 (in that order) were 10-20 fold higher in contaminated schools, while PCB153, PCB138 and PCB180 only were insignificantly higher. In another school where the PCB source was acoustic plates flame-retarded with high chlorinated PCBs, the blood levels of low-chlorinated PCB28 and PCB52 in pupils were not increased but levels of PCB138, PCB153 and PCB180 were increased 3-18 fold. In the Danish “Farum Midtpunkt” study the exposed dwellers had about four fold higher PCB concentrations in the blood than the non-exposed, in which only PCB138, PCB153 and PCB180 could be determined in the blood. In all exposed dwellers eight more PCB congeners were determined. An association between lower chlorinated PCB in plasma and exposure time in contaminated apartments was found both for low and high chlorinated PCBs, and the PCB concentration increased with age. Indoor air levels and plasma levels of residents was correlated for the PCB28.

Studies of toxicity of PCB in experimental animals

Most data has been generated for commercial PCB mixtures, and fewer data exist for the single congeners. In general, PCB mixtures or congeners readily absorbed orally, dermally and by inhalation. The absorption depends on the vehicle and the low-chlorinated congeners have a greater absorption. PCBs are, in general, very resistant to metabolism but depending on the structure of the congener small amount can be metabolized to hydroxy-PCBs which may be present in blood and are important for the toxicities associated with PCBs. The acute toxicities of commercial mixtures of PCB and non-dioxin-like PCB congeners are very low. However, the dioxin-like PCB77 and PCB169 were more than 1000 fold more acute toxic. After repeated administration of PCB mixtures and NDL-PCB congeners the toxic effects commonly observed include progressive weight loss, effects on the liver, skin, immune- and reproductive system and endocrine disruption. In 2-years feeding study with rats exposed to various *Aroclor mixtures* the lowest-observable-

adverse-effect-level (LOAEL) for liver effects was 1-2 mg/kg bw/day. Monkeys are more sensitive to the toxic effects of PCB than rodents and the lowest-observable-adverse-effect-level (LOAEL) was 10-20 times lower. In 90 days oral rat study of 7 single PCB congeners, the liver and thyroidea were the most sensitive organs. The LOAEL values determined were 0.3-0.4 mg/kg bw/day for NDL-PCBs (PCB28, PCB128, PCB153) and 0.8-170 µg/kg bw/day for DL-PCBs (PCB77, PCB105, PCB118 and PCB126, which the most toxic.

Immunotoxicity

The immune system is among the most sensitive of all organ systems to PCBs. Administrations of PCBs to experimental animals cause atrophy of the thymus gland and immunosuppression. In mice the DL-PCB77 congener was more distributed to the liver and thymus, and caused thymus atrophy at a lower dose, than that causing liver toxicity. The NDL-PCB52 had not such effect although the exposure was tenfold higher.

Endocrine effects

The endocrine system is an important target for PCBs. Some lower-chlorinated PCB congeners and metabolites exhibit weakly estrogenic effects, while higher-chlorinated ones are primarily anti-estrogenic. PCB mixtures and congeners effectively reduce circulating concentrations of thyroxine. Some PCB hydroxy- and sulfate metabolites bind to transthyretin in plasma of rats and mice and displace thyroxine from binding sites on transthyretin. Specifically, PCB118 caused morphological and functional deterioration of the rat thyroid in a two-year oral study. Chronic exposure to Aroclor 1254 exacerbates obesity-induced insulin resistance and hyperinsulinemia in both lean and diet-induced obese mice and exacerbated whole-body insulin resistance in obese mice. In mice fed a low-fat diet *but not a* high-fat diet, PCB-77 was associated with significant impairment of glucose and insulin tolerance, and PCB-126 significantly impaired insulin tolerance.

Reproductive toxicity

In many studies of PCB mixtures reproductive toxicity in animals was observed such as:

- Lower reproductive organ weights in exposed males
- Lower numbers of sperm in exposed males
- Altered estrous/menstrual cycles
- Lower number of exposed females mated
- Lower maternal weight gain during pregnancy
- Fewer completed pregnancies
- Greater incidence of malformations
- Fewer offspring/litter
- Lower birth weights of offspring
- Less postnatal survival of offspring
- Lower postnatal weight gain in offspring
- Lower reproductive organ weights in offspring
- Impaired function in offspring
- Permanent hearing deficits in offspring

The LOAELs for postnatal effects of PCB mixtures were at 0.25 mg/kg/day for rodents and 0.008 mg/kg/day for nonhuman primates. It shows that monkeys are more sensitive.

Neurotoxicity

Developmental neurotoxicity has emerged as a particularly vulnerable endpoint in chronic low-level PCB toxicity. This effect could be mediated by non-coplanar PCB's ability to alter the spatial and temporal fidelity of Ca^{2+}-signals. Experiments with rats confirmed that developmental exposure via the maternal diet to NDL PCB95 phenocopies the dendrite-promoting effects of Aroclor 1254. This effect was not seen by PCB66. Neonatal exposure to PCB28 and PCB52 (10 days of age) altered spontaneous motor activity, and for PCB 52 even impaired learning and memory functions in mice. In similar studies the dioxin-like PCB 105 and PCB126 had a neurotoxic effect in the brain and changed the behavior of mice. Some lower chlorinated NDL-PCBs, in particularly PCB28 and PCB52, can potentiate the human $GABA_A$ -receptor. PCB28 was more potent than PCB52 but there was an additive effect. Lower chlorinated NDL-PCBs also alter dopamine metabolism, inhibits dopamine transport and cause generation of reactive oxygen species. PCB28, PCB47 and PCB52 are incorporated into lipid bilayers, and mitochondrial- and endoplasmic reticulum membrane functions are disrupted. In ferrets that are mammalian carnivores with extra-large olfactory bulbs in the brain, it was shown that inhaled PCB PCBs pass into the dentrites of olfactory sensory neurons and are transported via olfactory axons directly to the bulbs, where they accumulate.

Mutagenicity

In general, PCB mixtures and congeners are not genotoxic; however, specifically Aroclor 1221 and 4-chlorobiphenyl (PCB3) were both mutagenic in the Ames *in vitro* test with *Salmonella typhimurium* and metabolic activation. Highly chlorinated PCB mixtures are routinely used in the Ames test and other test systems to activate liver enzymes preparations added for metabolism of the test substance. Thus, PCB may convert non-genotoxic xenobiotics into genotoxic metabolites.

Carcinogenicity in animals

The four commercial PCB mixtures which have been tested in long-term studies with rats all caused liver tumors in females and specifically Aroclor 1260 did it also in males. The DL-congeners PCB 126 and PCB118 have also been tested. PCB126 caused hepatocellular adenomas, cholangiocarcinomas, lung cystic keratinizing epitheliomas, and oral mucosa (gingiva) squamous-cell carcinomas in female rats, and PCB118 caused cancer of the liver, lung, and uterus and possibly of the pancreas plus a variety of other toxic effects at several sites of female rats. In addition PCB52, PCB77, PCB105, PCB126, and PCB153 are all promoters of liver tumors in mice initiated by dimethyl nitrosamine and sometimes they react synergistic.

Toxicological interactions

In a study PCB126 induced hepatotoxicity in rats which was modulated by dietary selenium. Exposure to PCB77 stimulates pro-inflammatory pathways in the vascular endothelium in mice, and therefore facilitates development of atherosclerosis, which could be prevented by supplement of *omega*-3 fatty acids. It has been shown that PCB138, PCB153, and PCB180 induce changes in the gut microbiome in mice with little exercise but not in mice exercising in a running wheel.

Toxicological mechanism

The main general toxicological mechanism by PCBs is induction of hepatic microsomal cytochrome P_{450} mono-oxygenase. This induction may generate reactive biological intermediates and interfere (potentiate or antagonize) with the actions of biological essential chemicals and xenobiotics. Since there will be more phenotypes there will be individual genetic differences in the response to PCB exposure. Dioxin-like PCB congeners are of the 3-methylcholanthrene type and binds to the aryl hydrocarbon receptor (AhR). PCB126

is most potent. Non-dioxin-like PCBs are of the phenobarbital type, and they also interact with the constitutive androstane receptor (CAR) and the pregnane xenobiotic receptor (PXR). Certain highly chlorinated NDL-PCBs (especially PCB 184 and PCB 197 but also PCB153) are potent activators of rodent PXR but antagonize its human ortholog: the steroid and xenobiotic receptor (SXR), inhibiting the detoxification of steroids, bioactive dietary compounds, and xenobiotics normally mediated by SXR. That shows that humans are more sensitive to NDL-PCB toxicity than rodents.

Epidemiology: Accidental exposures

The first known PCB accident was the Yusho mass food poisoning involving more than 1800 people, which was discovered in Western Japan in 1968. The poisoning was caused by a daily ingestion for about a half year of a commercial brand of rice cooking oil incidentally contaminated by large amount of PCBs from a leak in a heat-transfer installation for deodorizing the oil. This and many other accidents have involved used and heated PCB mixture which means an increased content of dioxin-like polychlorinated dibenzofurans, which are more toxic than pure PCB. The Yusho disease was characterized by severe acne-like eruptions of the skin, especially in the face. Other main signs or symptoms were: Dark-brown pigmentation of skin, nails, lips, and gingival and buccal mucosa, distinctive hair follicles, itching, increased sweating at the palms and swelling of the upper eyelids and increased eye discharge. Among the long-term effects was a small increased risk for cancer.

YuCheng happened in 1979 in Taiwan. It was again a leak in a heat-transfer installation but the PCB concentration in the rice oil was lower than in Japan. The disease symptoms were again chloracne, hyperpigmentation, dilation and hyper secretion of conjunctival glands etc. Among the known long-term effects was a 3 fold higher mortality of chronic liver disease and cirrhosis 13 years after the outbreak. The exposed YuCheng children had also poorer cognitive development. A 24-year follow-up study showed that the diabetes risk of women - but not men - was doubled. Women diagnosed with chloracne had even more than 5 fold higher risk for diabetes and more than 3 fold risk of hypertension compared to the chloracne free victims.

Epidemiology: Occupational exposures

PCB-exposed workers at power plants had increased mortality of melanoma and brain cancer which increased with cumulated PCB exposure. Workers at capacitor factories had elevated mortality among subgroups of long-term workers regarding all cancer, intestinal cancer; melanoma, brain and nervous system cancer. Furthermore, mortality of stomach and uterine cancer, prostate cancer, stomach cancer and multiple myeloma increased with estimated cumulative PCB exposure. In the beginning workers at PCB-renovation of buildings in Sweden were not well protected and were exposed to extremely high levels of PCB (280-370 µg PCB/m^3), and effects on the function of the thyroidal gland were reported. Some teachers in PCB polluted indoor environment in schools in Germany expressed subjective health complaints, which was assessed by standardized neuropsychological testing. It was concluded that chronic inhalation of low chlorinated PCBs that involved elevated blood levels was associated with a subtle attenuation of emotional well-being and attentional function. Office workers in Germany had more subjective health complaints (exhaustion and stomach, limb and cardiac complaints) than in controls. There was no correlation between these complaints and blood concentration of low-chlorinated PCBs. However, there were analytical problems, since PCB52 could not be quantified in the blood.

Epidemiology: General population

A general problem with studies of the general population is that the PCB levels here are rather small, and PCB is not alone but together with many other xenobiotics so interactions are likely, and it is difficult to establish a definite cause-effect relation. The most abundant PCB congeners in the general population are the more persistent higher chlorinated congeners from food intakes.

Reproduction

Several studies have shown that PCB may interfere with the adult reproductive system. It was found that for samples with low sperm count, there was a decrease in sperm motility with increasing concentrations of the sum of PCB153, PCB138 and PCB118.Maternal low-level exposure to PCB impairs fetal growth, means shorter duration of pregnancy and decreases the birth weight of her newborns. For women undergoing artificial fertilization, there was a double risk of pregnancy loss. The human placenta is clearly a target of PCB toxicity, and current environmental PCB exposure levels are a risk to reproductive health.

Neurotoxicity

The developing fetus and infants are most vulnerable to exposure for PCB. There is growing evidence that PCB may affect transient neurodevelopment and neuropsychological function in children. PCB concentrations were also associated with diminished mental and psychomotor development. Thyroid dysfunction may be a mediator of organochlorine neurotoxicity in preschool children. PCB may be a risk factor in Parkinson's disease. The mechanism may be that NDL-PCBs inhibit the dopamine transporter. Animal experiments have shown that PCB mixtures can decrease the expression of dopaminergic markers, the PCB-153 concentration was elevated in post-mortem human brains from Parkinson patients, and a cohort of heavily PCB-exposed female workers had increased risk for catching this disease, dementia and amyotrophic lateral sclerosis.

Endocrine disruption

Reduction of sex hormone levels in serum was associated with dioxins and DL-PCBs, and testosterone reduction was more pronounced in cord serum of female and estradiol reduction in that of male newborns. Higher prenatal PCB exposure was associated with lower serum concentrations of both luteinizing hormone (LH) and testosterone, and sex hormone binding globulin (SHBG) was positively associated with both prenatal and concurrent PCB exposures. Hydroxy-metabolites of coplanar DL-PCB have a structure resembling thyroxine (T_4) and may bind to its transport proteins and reduce thyroxine levels in the blood. In a population in Germany around a toxic waste incinerator was found a significant positive association with PCB118 and thyroidea stimulating hormone (TSH), and a negative relationship of PCB138, PCB153, PCB180, PCB183 and PCB187 to free triiodothyronine (FT_3).

The classical dose-response relationship is not always relevant for endocrine disruption. Small changes may have a big effect for endocrine disruptors, because a low dose of a hormone or hormone-mimicking chemical has a disproportionately large effect on receptor occupancy, while greater doses have a relatively smaller effect, as receptors become saturated.

Effects on obesity

Chemical exposures may increase the risk of obesity by altering the differentiation of adipocytes or the development of neural circuits that regulate feeding behavior. The effects may be most apparent, when the developmental exposure is combined with consumption of a high-calorie, high-carbohydrate, or high-fat

diet later in life. It was shown in a study from USA that background levels of PCB may affect body size of white girls at puberty. A study from Belgium found an association between increasing concentrations of PCB (and DDE) in cord blood and increasing Body Mass Index of 1-3 years old children. A positive association has been found between PCB105 and PCB118 in blood plasma and in both the most harmful visceral adipose tissue and in subcutaneous adipose tissue.

Effects on diabetes

In the last years dozens of studies have reported association between body concentrations of POPs including PCBs and the metabolic syndrome, insulin sensitivity and insulin secretion. This diabetic effect may occur at low doses similar to current human exposure levels, possibly through endocrine disruption, and may play a role in the current epidemic of type-2 diabetes, which mainly have been attributed to obesity. Some of the studies supporting the link between PCB and type-2diabetes are one examining a highly PCB-exposed population, where the most PCB exposed quintile women had almost three folds higher risk for type-2 diabetes. Further, in a study of Native Americans there was observed an almost 4 folds higher risk of type-2 diabetes in the most PCB exposed people. The association with PCB74 was stronger than for PCB153. In Faroe Island people over 70 years old with type-2 diabetes or impaired fasting glycemia tended to have higher PCB concentrations and higher past intake of traditional foods. Both for persons with normal weight, overweight and obese people in Spain, there was an association between increasing PCB (PCB118, PCB138, PCB153 + PCB180) in blood serum and type-2 diabetes. For obese persons with the highest PCB concentration the risk for diabetes was 9 fold higher. The conclusions from a recent expert workshop was that the overall evidence from available studies was sufficient for a positive association of some organochlorine POPs, including PCB, with type-2 diabetes but these data were not sufficient to establish causality.

Immunotoxicity

Increasing evidence suggests that PCBs can cause dysregulation of the immune system through immunosuppression and immune stimulation/inflammation. PCB exposure has been associated with an increased incidence of respiratory infections, ear infections, influenza, and chicken pox in healthy Dutch and Inuit preschoolers; children of capacitor manufacturing workers, particularly those breast-fed for lengthy periods; and children prenatally exposed to PCB- and PCDF-contaminated rice oil during the YuCheng poisoning incident. PCB exposure has also been associated with insufficient response to vaccination in two birth cohorts from the Faroe Islands with pre- and postnatal PCB exposure from dietary consumption of whale blubber. In Slovakia, a country with high background exposure for PCB from previous industrial production and use, it was observed in a group of 1134 mother-child pairs that high maternal PCB (15 congeners) blood concentration was associated with reduced thymus volume at birth.

Cardiac toxicity

Already in a very early study a positive association between PCB in blood serum and elevated blood pressure, serum cholesterol and γ-glutamyl transpeptidase level was shown. In NHANES 1999-2004 a significant association was also observed between elevated blood pressure and serum levels of dioxin-like PCB74, PCB118 and PCB126. Among Inuit's from Canada total PCB as well as DL-PCBs was associated with hypertension. In an area with high PCB contamination in soils total serum PCB concentration was the strongest determinant of blood pressure of the covariates studied in the population - other than age. In a study of the NHANES 1999-2002 cohort PCB congeners 156 (dioxin-like), 138, 153, and 170 were associated with self-reported cardiovascular diseases among females but not males. In Sweden circulating levels of

PCB congeners 153, 156, 157, 170, 180, 206, and 209 were associated with increased atherosclerotic plaques formation and increased risk of developing or progression of stroke in an elderly population.

Cancer

In various groups of PCB-exposed workers, increased mortality from melanoma, brain cancer and intestinal cancer have been reported. Mortality of uterine cancer, prostate cancer, stomach cancer and multiple myeloma increased with estimated cumulative PCB exposure.

The International Agency for Research on Cancer (IARC) has made a cancer assessment of PCB four times. In 1978 it was concluded that PCBs should be regarded as carcinogenic to humans. In 1987 the evaluation was that PCB was probably carcinogenic to humans (Group 2A) and in 2012 the evaluation was that PCB was carcinogenic to humans (Group 1). In the most recent evaluation, in February 2013 the IARC working group concluded that there was sufficient evidence of carcinogenicity in humans, and PCBs were classified as carcinogenic to humans (Group 1). Dioxin-like PCBs were classified in Group 1 based on strong evidence for multiple mechanisms of carcinogenesis.

The most recent evaluation of PCBs considered the mixture of congeners, since the carcinogenicity is not known to be limited to a small number of congeners, and because human exposures to PCBs, whether from indoor air or from other sources, always involve mixtures of many congeners. Thus, although IARC does not consider source attribution in their evaluations, the current classification of PCBs also applies to exposures from construction materials, which may be one of the important sources of exposure.

Comparison of food intakes and indoor exposure

The PCB average intake via food in Denmark has recently been estimated to recently to 9 ng PCB/kg b. w./day or 630 ng PCB/ day for an adult person weighing 70 kg. For indoor air concentration of 300-3 000 ng PCB/m^3 and if a person inhales 20 m^3 air daily, then the intake with indoor air will be 6 000-60 000 ng PCB_6 or 10-100 fold the food intake, if a person is exposed to PCB indoors for the whole day. However, intake from food and indoor air cannot directly be compared because of the different congeners present but the indoor exposure will be additional intake of PCB and increase body burden.

Tolerable daily intake

WHO has recommended a tolerable daily intake (TDI) of 20 ng PCB/kg b. w. which was derived from a LOAEL of 5 µg/kg b. w. in monkeys exposed to a commercial mixture of PCBs (Aroclor 1254), and EU has established a tolerable weekly intake (TWI) of 14 pg TEQ/kg b. w. for dioxin-like-PCBs. Dietary exposure in Denmark to dioxins and DL-PCB as well as to NDL-PCB exceeds the TDI/TWIs for a small fraction of the population, and mainly for children.

Actions values for indoor air

Already in 1996 limit values for 24 hours indoor exposure to PCB was established in Germany. The annual mean action value was 300 ng/m^3, and the intervention value was 3000 ng/m^3 (3 µg/m^3). The PCB concentration was calculated as PCB_6 multiplied with a corrections factor of 5. The toxicological basis was an old TDI for technical PCB mixture of 1-3 µg PCB/kg bw/day derived from an old rat experiments. More recent studies have shown that PCB has adverse effects in rats exposed to 900 ng PCB/m^3, and in monkeys with a daily intake of 5 µg PCB/kg bw/day. Air concentrations were calculated based on body weight of 60

kg and an inhalation rate of 20 m^3/24 hours. The health authority in Schleswig-Holstein has later developed more detailed recommendations of sanitation activities as a supplement.

Concluding remarks on data for the single congeners

The most relevant PC B congeners in the indoor climate are normally the low-chlorinated and most volatile congeners. Only a fraction of these are normally measured routinely in indoor air. Measured are mainly PCB28, PCB58 and partly PCB101 and PCB118. Of these PCB52 is often measured in the highest concentration.

Some of the missing congeners, which have been measured only in a few studies, are PCB1, PCB4, PCB8, PCB17, PCB18, PCB20 PCB31, PCB44, PCB49 and PCB70. In one study the sum of the last 7 congeners was more than the double of PCB28 + PCB52. The health hazard of these missing congeners will be difficult to evaluate because of the lack of test results for these chemicals.

However, the low-chlorinated congeners are easier metabolized and some are genotoxic. For PCB28 and PCB52 there exist much data. Both congeners are found in blood serum from the general population but the concentration of PCB28 may be 30 fold higher in exposed populations. There was a clear correlation between PCB28 in indoor air and PCB28 in the dwellers blood plasma. The elimination half-lives of PCB28 and PCB52 are shorter than the higher chlorinated congeners.

PCB28 and PCB52 are NDL-PCBs and have several orders of magnitude lower general toxicity than the DL-PCBs but the same general toxicity as the high-chlorinated NDL-PCBs. The main target for the dioxin-like low-chlorinated, such as PCB77, was the liver and thymus. In contradiction PCB28 and PCB52 target the nervous system, and PCB28 is more neurotoxic than PCB52 but there are additive effects.

Neonatal exposure to PCB28 and PCB52 (10 days of age) altered spontaneous motor activity, and PCB52 even impaired learning and memory functions in mice. These two congeners also concentrate most in the olfactory bulbs in ferrets.

PCB28, PCB47 and PCB52 incorporate into lipid bilayers and with its bulky, three-dimensional *ortho*-substituted congener structure it disrupts mitochondrial and endoplasmic reticulum membrane function to a greater degree than coplanar congeners.

Regarding endocrine effects PCB118 is very potent and led to dose dependent changes in enzyme and hormone levels, including decrease of serum total thyroxine. A positive association has been showed between PCB118 in blood plasma and the most harmful *visceral adipose tissue* and *subcutaneous adipose tissue*. There was a significant association between elevated blood pressure and serum levels of among others, PCB118. PCB-118 is also considered a human carcinogen. PCB52 and many other NDL-PCBs are tumor promoters.

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Glossary

ADHD	Attention deficit hyperactivity disorder
AhR	Aryl hydrocarbon receptor
ALT	Alanine aminotransferase
AMAP	Arctic Monitoring and Assessment Program
AT	Adipose tissue
Atm	Atmosphere
ATSDR	Agency of Toxic Substances and Disease Registry
BMI	Body Mass Index
BW	Body weight
CAR	Constitutive androstane receptor
COMT	Catechol-O-methyl transferase
CVD	Cardiovascular diseases
CYP	Cytochrome P_{450}
DDE	Dichloro-diphenyl-dichloroethylene
DDT	Dichloro-diphenyl-trichloroethane
DHEA-S	Dehydroepiandrosterone
DIN	Deutsches Institut für Normung
DL	Dioxin-like
EFSA	European Food Safety Authority
EU	European Union
FDA	U.S. Food and Drug Agency
German EPA	Umweltbundesamt
GIS	Geographic Information System
IARC	International Agency for Research on Cancer
IQ	Predictors of intelligence

IUPAC	International Union of Pure and Applied Chemistry
LAGA	Länderarbeitsgemeinschaft Abfall
LH	Luteinizing hormone
LOAEL	Lowest observed adverse effect level
NDL	non-dioxin-like
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observed adverse effect level
NHL	Non-Hodgkin Lymphoma
NTP	National Toxicology Program (US)
OCDD	Octachlorodibenzo-*p*-dioxin
OECD	Organization for Economic Cooperation and Development
OH-PCB	Hydroxy-PCB
Pa	Pascal
PAH	polycyclic aromatic hydrocarbon
PBB	Polybrominated biphenyl
PCB	Polychlorinated biphenyl
PCB_6	PCB28 + PCB52 + PCB101 + PCB138 + PCB153 + PCB180
PCB_7	PCB_6 + PCB118
PCDD	Polychlorinated dibenzo-*p*-dioxin
PCDF	Polychlorinated dibenzofuran
PCN	Polychlorinated naphthalene
PCQ	Polychlorinated quaterphenyl
PCT	Polychlorinated terphenyl
PEN	PCB Elimination Network
PlGF	Placental Growth Factor
POP	Persistent organic pollutant

PUF	Polyurethane foam
PVC	Polyvinyl chloride
PXR	Pregnane xenobiotic receptor
REP	Relative Effect Potency
RyR	Ryanodine receptors
SAT	Subcutaneous adipose tissue
ST	Syncytiotrophoblast
SXR	Steroid and xenobiotic receptor
TDI	Tolerable daily intake
T_3	Triiodothyronine
T_4	Thyroxine
TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin/"dioxin"
TEF	(Dioxin) Toxicity Equivalent Factors
TEQ	Dioxin equivalent
TSH	Thyrotropin, thyroidea stimulating hormone
TTR	Transthyretin
TWI	Tolerable weekly intake
UNEP	United Nations Environment Program
USEPA	United States Environmental Protection Agency
VAT	Visceral adipose tissue
WHO	World Health Organization